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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).
[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).
[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

*Abbreviations* are used freely in *Tetrahedron*, particularly in setting the experimental section. For the most part these are not followed by a full stop (period). Among the more commonly used abbreviations, these may be listed:

g kg mm cm ml cc $cm^3$ sec min hr $n_D^{25}$ $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but $in^2$.

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{12}H_{12}O_4N$ requires C, 63·2; H 5·3%).

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# STUDIES IN SESQUITERPENES—XVIII*

## THE PROTON MAGNETIC RESONANCE SPECTRA OF SOME SESQUITERPENES AND THE STRUCTURE OF HUMULENE

SUKH DEV
Department of Organic Chemistry, Indian Institute of Science, Bangalore

(*Received* 22 *September* 1959)

**Abstract**—The nuclear magnetic resonance spectra of longifolene, zerumbone, humulene, and their hydroderivatives have been studied in order to gauge the potentialities of this new tool in the field of sesquiterpenes. On the basis of present study, it has been possible to unequivocally fix the positions of the ethylene linkages in humulene and thus provide a straightforward solution of this hitherto unsolved problem.

IN recent years high-resolution nuclear magnetic resonance (NMR) spectroscopy has been applied with singular success in solving certain structural problems in organic chemistry.[1] In the present communication the results of the application of NMR to certain sesquiterpenes are discussed. In the first instance spectra of longifolene and zerumbone were studied in order to seek correlations with the known structures of these substances, and later on the method was extended to finally settle the structure of humulene.

*Longifolene*

The total structure I of longifolene is based essentially on the elegant X-ray crystallographic study of longibornyl chloride by Moffett and Rogers,[2] although excellent chemical evidence has been provided for certain important structural features by Naffa and Ourisson.[3–5] The proton NMR spectrum of longifolene is in complete accord with the structure I. The spectrum, with the peak

I

assignments, is shown in Fig. 1. The integerated areas under the various peaks are

* Part XVII: *Tetrahedron* **8**, 42 (1960).

[1] *a* W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* **77**, 2451 (1955); *b* E. J. Corey, H. J. Burke and W. A. Remers, *Ibid.* **77**, 4941 (1955); *c* A. T. Bottini and J. D. Roberts, *J. Org. Chem.* **21**, 1169 (1956); *d* N. L. Allinger, *Ibid.* **21**, 1180 (1956); *e* M. G. Ettlinger and F. Kennedy, *Chem. & Ind.* 166 (1956); *f* J. Gripenberg, *Acta Chem. Scand.* **10**, 487 (1956); *g* E. F. Silversmith and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 4023 (1956); *h* E. E. van Tamelen, S. H. Levin, G. Brenner, J. Wolinsky and P. Aldrich, *Ibid.* **80**, 501 (1958); *i* K. L. Rinehart, W. A. Nilsson and H. A. Whaley, *Ibid.* **80**, 503 (1958).
[2] R. H. Moffett and D. Rogers, *Chem. & Ind.* 916 (1953).
[3] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115, 1410 (1954).
[4] P. Ourisson and G. Ourisson, *Bull. Soc. Chem. Fr.* 1415 (1954).
[5] G. Ourisson, *Bull. Soc. Chim. Fr.* 895 (1955).



1

approximately* in accord with the populations of the various types of hydrogens in I. A point of special interest is that, as expected,[6] the allylic tertiary hydrogen (84·2 cps) is well-separated from the remaining two tertiary protons (102·6 cps) of longifolene. That these assignments are correct is borne out by the NMR spectrum of longifolane (Fig. 2), wherein the '84·2 cps band' has disappeared. There is no spin–spin splitting for the methyl hydrogens, and this is as it should be, since the methyl groups are attached to carbon atoms carrying no protons. It may be noted that, as

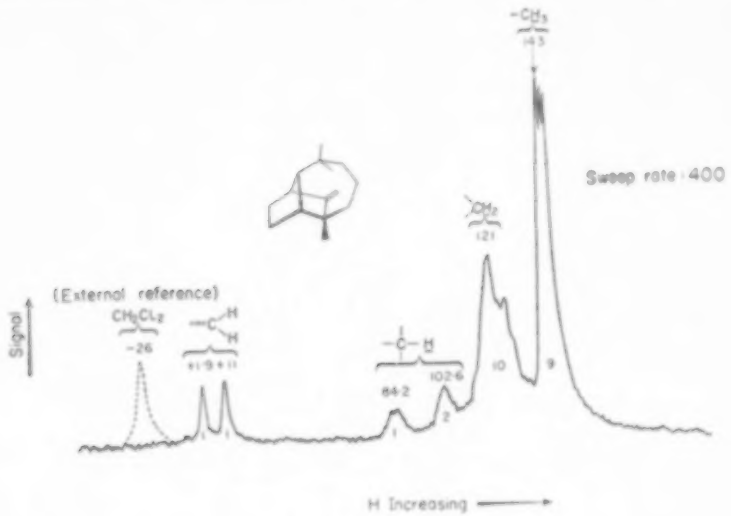


FIG. 1.

expected, such a splitting appears in the case of longifolane (the doublet at 151·7 and 144·3 cps, the 144·3 cps peak would also contain the other nine methyl protons). Another important structural feature of I is also clearly reflected in the NMR spectrum; in longifolene, out of the two, otherwise chemically equivalent, olefin protons, one is diamagnetically more shielded due to the occurrence of a fused 7-membered ring in its immediate neighbourhood ('field effect' due to steric interactions[7]), and this should explain the presence of two olefin proton peaks at 1·9 and 11 cps.† That these bands represent a true chemical shift was proved by the field-dependence of the shift; when the spectrum was determined at 16 mc rf., the olefin protons appeared at

* The numbers shown under the various peaks in Fig. 1, represent the number of protons, on the basis of structure I, to be associated with each peak. The actual values were as follows: The ratio of saturated to olefinic protons was calculated from the spectra taken at different sweep rates, and with the sample not spinning (this gave smooth curves with finer resolution missing, but the olefinic and saturated protons were well-separated; area measurement on such curves was easier); the observed ratio varied from 12·5 to 10·8 (calc. 11). From the high resolution curve (Fig. 1), the number of methyl hydrogens was found to be 9·5 (calc. 9). The areas were determined by the weighing method.

† The protons of an asymmetric disubstituted ethylenic linkage, by virtue of electron release by the alkyl groups, would be more shielded as compared to a symmetrically disubstituted (or more highly substituted) olefinic linkage and, hence, resonance will occur at higher field strength, as in the case of longifolene. This is borne out by the data available in *A catalogue of the nuclear magnetic resonance spectra of hydrogen in hydrocarbons and their derivatives*. Humble Oil and Refining Co., Texas (1959).

[6] E.g. cf. the spectrum of methyl linolenate [*Tech. Information Bulletin from the Laboratories of the Instrument Div., Varian Associates* **2**, No. 3, 10 (1959)]; N. F. Chamberlain, *Analyt. Chem.* **31**, 56 (1959).

[7] W. D. Kumler, J. N. Shoolery and F. V. Brutcher, *J. Amer. Chem. Soc.* **80**, 2533 (1958).

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—15·4 and —11·2 cps, and thus, the peak separation dropped from 9·1 cps to 4·2 cps, which is in good accord with the calculated value of 3·6 cps.

*Zerumbone*

On the basis of chemical evidence, zerumbone has recently been shown[8] to be II. A study of its NMR spectrum appeared to be of special interest, because of the

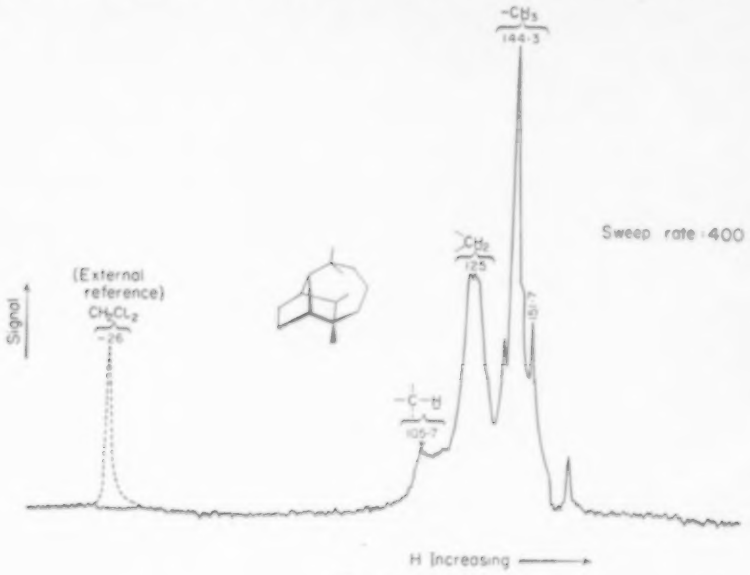
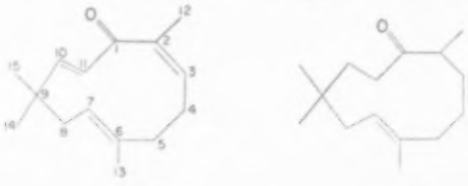



FIG. 2.

possibility of gaining some information from such a study about the precise location of the ethylenic linkages in the closely related hydrocarbon, humulene (*vide infra*). The NMR spectrum of zerumbone (Fig. 3) shows an excellent resolution into different types of protons and the different peaks would appear to correspond to the number



II III

of protons indicated under each band.* Clearly, the 147·7 cps resonance peak at the highest field strength is to be ascribed to the *gem*-dimethyl groups,[9] while the bands at 132·7 and 124·8 cps are each assignable separately to the methyl groups on the ethylenic linkages.[1d,9] This chemical shift (7·9 cps) between these two methyl groups probably arises due to some *trans*-annular shielding of one of the methyl groups; the carbonyl

* The values in parentheses show the relative areas from actual area measurements from the spectrum, whereas the other numbers represent the number of protons expected to occur under a given peak, according to the structure of the compound under discussion. These remarks also apply to Figs. 4–6.

[8] Sukh Dev, *Chem. & Ind.* 1051 (1956); *Tetrahedron* **8**, 171 (1960).

[9] L. H. Meyer, A. Saika and H. S. Gutowsky, *J. Amer. Chem. Soc.* **75**, 4567 (1953).

group is hardly expected to affect the $C_{12}$ methyl by an inductive mechanism. The next set of peaks (104·3 and 112·2 cps) is readily assignable to the six methylene protons, which are not overlapping the $C_{12}$ and $C_{13}$ protons, by virtue of their being entirely situated on allylic positions.[6] The last group of resonance peaks (—37·9, —23·7, —14·2 and —6·3 cps) represents the remaining four olefinic protons. From the area measurements, it would appear that the —37·9 cps peak contains three protons, which would be the hydrogens on the 3, 10, and 11 positions, the remaining

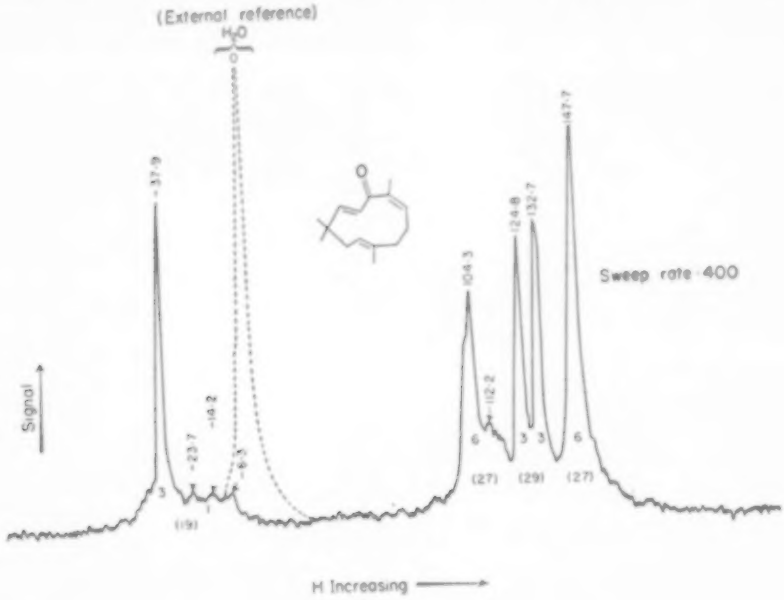



FIG. 3.

ethylenic proton, which is not subject to the diamagnetic unshielding by the carbonyl, occurs as expected, at a higher field strength. It is rather surprising that no chemical shift between the α-H (at $C_{11}$), and the β-protons (at $C_3$ and $C_{10}$) which are subject to a greater unshielding by the carbonyl by a congugative electron displacement, is observed.*

These assignments for zerumbone, which are self-consistent, are amply confirmed by the NMR spectra of tetrahydrozerumbone III (Fig. 4), hexahydrozerumbone and deoxyhexahydrozerumbone (humulane, Fig. 6). From the area measurements on Fig. 4, it is clear that the $C_{13}$ methyl-protons occur at 127 cps; it is to be noted that this band is now being overlapped by the absorption due to some methylene protons which are no longer allylic. Tetrahydrozerumbone has only one olefinic proton, which has shown up clearly as a triplet (spin-spin splitting due to $C_8$-methylene hydrogens) with the centre at —15·3 cps. This confirms the ethylene proton assignments in zerumbone. The peaks at 116·3 and 107 cps would represent the methylene groups at $C_5$, $C_8$ and $C_{11}$, whereas the 99·5 cps band would appear to be a triplet (due to the tertiary proton at $C_2$) superimposed on the rising absorption of the

* E.g. the α-olefinic proton in methyl crotonate shows up at —34 cps, while the β-hydrogen appears at —89 cps.

methylene protons. This appears to be confirmed by the NMR spectrum of hexahydrozerumbone, which has peaks, besides those due to methyl and methylene hydrogens (at 156·1, 146·9 and 137·7 cps), at 123·9 (a septet) and 99·5 cps (a triplet), and which from peak inspection would correspond to two and one protons respectively, and thus would be assignable to the $C_{11}$-methylene protons and the tertiary hydrogen at $C_2$ respectively. Finally, the NMR spectrum of humulane clearly shows the two

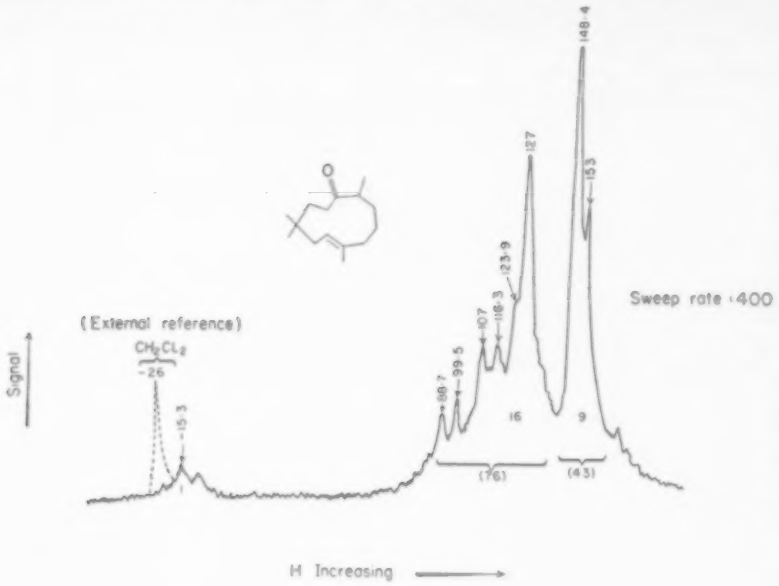



FIG. 4.

types of protons with the expected populations. As a part of special interest, it may be noted in the present series, that as the $\pi$-electron centres are removed from the molecule the methyl hydrogens get more and more shielded (147·7 → 156 cps), this possibly has its origin in the expected progressive crowding in the ring.

*Humulene**

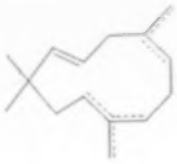
Various structures (IV[10], V[11], VI[12], VII[13]) have been proposed for humulene. While the nature of the carbon-skeleton is well-established,[14] the position of the olefinic linkages is not known with any certainty. Humulene is known to yield *as*-dimethylsuccinic acid on oxidation with chromic acid[15] or ozone,[16,17] and formaldehyde[16,17] and laevulinic aldehyde[17,18] have also been isolated after ozonolysis. These

* A preliminary note appeared in *Tetrahedron Letters* No. 7, 12 (1959).

[10] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* **16**, 639 (1951).
[11] G. R. Clemo and J. O. Harris, *Chem. & Ind.* 799 (1951); R. W. Fawcett and J. O. Harris, *Ibid.* 18 (1953); *J. Chem. Soc.* 2673 (1954).
[12] Sukh Dev, *Curr. Sci.* **20**, 296 (1951).
[13] P. Clarke and G. R. Ramage, *J. Chem. Soc.* 4354 (1954).
[14] F. Sorm, M. Streibl, V. Jarolim, L. Novotny, L. Dolejs and V. Herout, *Coll. Czech. Chem. Comm.* **19**, 570 (1954).
[15] A. C. Chapman, *J. Chem. Soc.* **83**, 505 (1903).
[16] F. Sorm, J. Mleziva, Z. Arnold and J. Pliva, *Coll. Czech. Chem. Comm.* **14**, 699 (1949).
[17] G. R. Clemo and J. O. Harris, *J. Chem. Soc.* 22 (1951).
[18] E. R. Klein and N. F. Lahey, *Chem. & Ind.* 760 (1951).

data are readily understandable, if humulene is considered to be IV or VII, with the provision that bond-mobility (as in VI) is involved in some of its oxidative degradations. Such a behaviour has previous precedent.[19] The presence of a semi-cyclic methylene

IV



V

VI

VII

group in purified humulene has been claimed[16] on the basis of quantitative ozonolysis and infra-red spectral measurements. On the other hand, Clarke and Ramage[13] favour the structure VII* on the basis of oxidative degradation of some crystalline humulene derivatives.

Ozonolysis of certain compounds lacking in an asymmetric disubstituted ethylenic linkage, has been known to yield formaldehyde or formic acid.[20] On the other hand some compounds containing such a linkage have failed to give more than a trace of these products after ozonolysis.[1c,3,21] Similarly, at least some compounds without $RR'C{=}CH_2$ linkage have been shown[22] to absorb, often strongly, around 890 $cm^{-1}$ in the infra-red. In view of these, it seemed desirable to re-examine the whole problem by a method which could offer an unequivocal answer. In this connexion, the NMR spectrum of humulene has been studied, especially because in the NMR spectrum of zerumbone, the closely related sesquiterpene ketone, the various methyl and methylene protons were so nicely resolved.

The NMR spectrum of humulene, with the proton populations of the various peaks, is shown in Fig. 5. It is at once apparent from this spectrum, that the methyl and methylene proton region of the NMR curve of humulene is *almost identical* with that of the corresponding region in the zerumbone spectrum (cf. Fig. 3), both as regards the relative disposition of the peaks as well as the area under each peak

* Very recently [R. P. Hildebrand, M. D. Sutherland and O. J. Waters, *Chem. & Ind.* 489 (1959)] fresh chemical evidence, based on $LiAlH_4$-reductive cleavage of the humulene ozonide, in favour of structure VII has been published.

[19] R. Kuhn and H. Roth, *Ber. Dtsch. Chem. Ges.* **65**, 1285 (1932); A. E. Bradfield, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 309 (1935); G. R. Ramage, R. Whitehead and B. Wilson, *Ibid.* 4341 (1954).

[20] J. Knights and E. S. Waight, *J. Chem. Soc.* 2830 (1955).

[21] J. T. Gragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer. Chem. Soc.* **75**, 3344 (1953).

[22] For example, n-octane, 3-ethylhexane, 3-methyl-3-ethylpentane, geranylamine hydrochloride [D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.* 915 (1950)], $\Delta^3$-*p*-menthene [R. L. Frank and R. E. Berry, *J. Amer. Chem. Soc.* **72**, 2985 (1950)], and α-pinene [J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* **15**, 160 (1950)] absorb strongly near 890 $cm^{-1}$, although the grouping $RR'C{=}CH_2$ is certainly absent.

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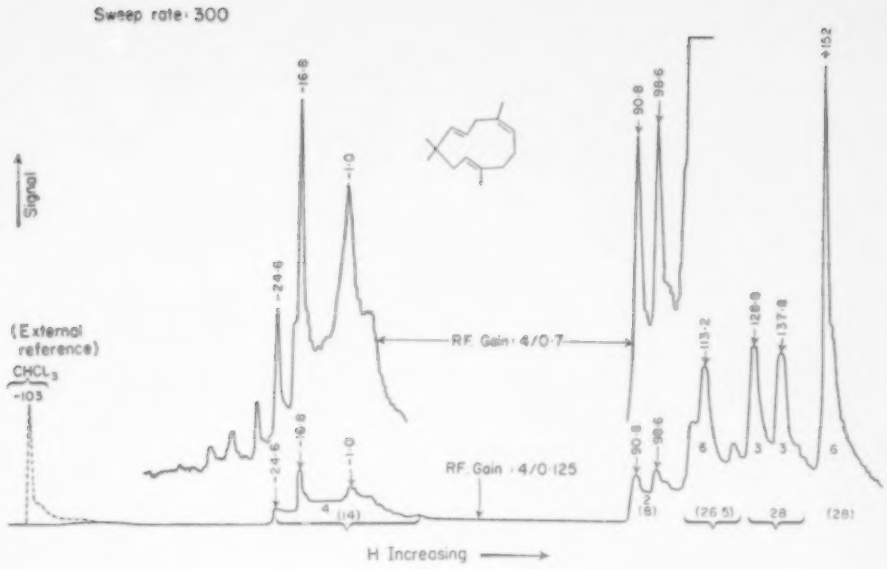


FIG. 5.

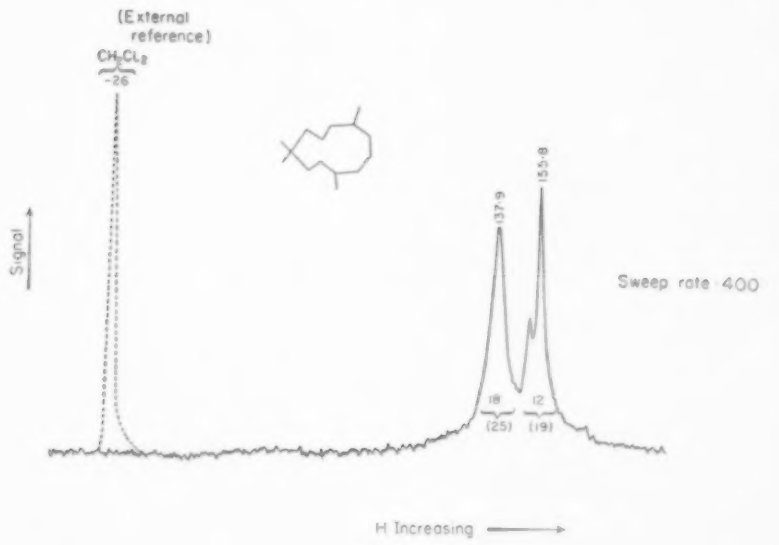


FIG. 6.

(average shift of these bands relative to those of zerumbone is ~6 cps). This forces us to the only conclusion that humulene, like zerumbone, has *four methyl groups* and all of its methylene groups are located at allylic positions. This is in accord with structure VII only. The 'new' methylene group at position 9 in humulene, as expected,[6] showed up at a still lower field strength (peaks at 90·8 and 98·6 cps with the areas approximately in the ratio 1 : 1), and the olefinic protons formed a complex multiplet in the expected region. As a point of further evidence in favour of structure VII, it

may be noted that from the relative areas of the olefinic and 'saturated' protons, the number of ethylenic hydrogen atoms in humulene works out to be 3·3, a figure which is closer to that required for VII as compared to that required for IV.

As discussed earlier, the presence of a band around 890 $cm^{-1}$ in the infra-red spectrum of humulene does not constitute a strong argument for the presence of

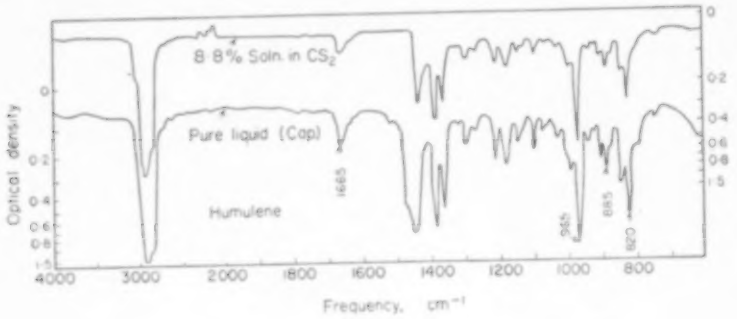


FIG. 7.

$RR'C{=}CH_2$ group. We have re-examined quantitatively the infra-red absorption of humulene (Fig. 7), especially because from the published spectra[16] of humulene and caryophyllene (in which the presence of the grouping $RR'C{=}CH_2$ is based on sound chemical evidence), the absorption of humulene around 890 $cm^{-1}$ appeared to be much smaller as compared to that of caryophyllene in the same region. As would be clear from an examination of the results (Table 1), the intensity of the 890 $cm^{-1}$

TABLE 1. APPARENT MOLECULAR EXTINCTION CO-EFFICIENTS OF SOME RELEVANT BANDS IN THE INFRA-RED ABSORPTION OF HUMULENE

| Peak ($cm^{-1}$) | Assignment | No. of groups | $\varepsilon^{(a)}$ | |
|---|---|---|---|---|
| | | | Found | Average val. from lit.[23] |
| 1665 | $RR'C{=}CHR''$<br>$RHC{=}CHR'$ (*trans*-) | 2<br>1 | 20·8 | $RR'C{=}CHR''$ ?<br>$RHC{=}CHR'$ ~2<br>$RR'C{=}CH_2$ 30–45 |
| 965 | $RHC{=}CHR'$ | 1 | 125 | 100–110 |
| 820 | $RR'C{=}CHR''$ | 2 | 64 | 33–50 |
| 885* | — | — | 32 | $RR'C{=}CH_2$ 120–160 |

* Many *trans*-olefins absorb in this region.[23c]

[23] *a* R. N. Jones and C. Sandorfy in A. Weissberger's, *Technique of Organic Chemistry* Vol. IX, pp. 367–384. Interscience, New York (1956); *b* D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.* 915 (1950); *c* H. L. McMurry and V. Thornton, *Analyt. Chem.* **24**, 318 (1952).

peak is not consistent* with the presence of $RR'C{=}CH_2$ system in humulene. Thus the evidence presented in this paper allows the unequivocal formulation of humulene as VII. Like zerumbone, the $\Delta^{10}$-ethylenic bond in humulene has a *trans*-configuration, and the precise steric arrangement of the other two olefinic linkages remains as yet uncertain. This structure of humulene is directly related to that of zerumbone by an oxidation–reduction system, and we are currently trying to effect such interconversions.

Theoretically, humulene now becomes biogenetically related[24] to farnesol by a simple path involving no rearrangement of the ethylenic linkages.

## EXPERIMENTAL

*Materials.* Longifolene, zerumbone and their derivatives employed for the determination of their NMR spectra were all purified samples and their preparation has been described previously (Parts XVI and XVII of this series).

Humulene was isolated from the essential oil of *Zingiber zerumbet*[12] and after precise fractionation had: b.p. 114–115°/5 mm, $n_D^{25}$ 1·5015, $[\alpha]_D^{25}$ −0·31, *nitrosochloride*[25] m.p. 175–176°, *trioxide*[16] m.p. 122°.

*Proton magnetic resonance spectra.* All proton magnetic resonance spectra were determined at 40 mc rf., except when stated to the contrary, with a Varian Model V-4300B high-resolution spectrometer fitted with a field-sensing stabilizer. Chemical shifts were measured by superimposing an audiofrequency, and using the side bands which develop, to determine the chemical shifts between two signals in cycles per second.[26] The compounds were measured as 25 per cent solutions in carbon tetrachloride. An external reference was employed using a concentric-tube cell:[27] the reference used in each case has been indicated on the NMR curve, the solid line represents the signal without the reference compound, while the broken line shows how the signal was modified, when the reference compound was also introduced in the magnetic field. All chemical shifts described herein have been expressed relative to water (zero standard), though for most of the measurements the actual external reference used was other than water; in such cases the shifts in cps relative to water were figured out by subtracting from the observed shifts (relative to the actual standard) the chemical shift in cps between water and the actual reference compound (for $CH_2Cl_2$ 26 cps and for $CHCl_3$ 103 cps; these values were obtained from actual runs). All spectra were taken at 25°.

*Infra-red spectra.* These were determined with a Perkin–Elmer double-beam instrument, both on the pure liquid and on its 8·8 per cent solution in $CS_2$. Sodium chloride optics were employed.

*Acknowledgements*—This work was carried out at the Noyes Chemical Laboratory, University of Illinois, Urbana, and the author wishes to place on record his sincere gratitude to Prof. E. J. Corey for these facilities. The NMR spectra were kindly obtained by Mr B. A. Shoulders.

* The intensity of the 890 $cm^{-1}$ band is known to be considerably reduced in certain compounds containing $RR'C{=}CH_2$ grouping [D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.* 3314 (1958); L. Dolejs, M. Soucek, M. Horak, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2195 (1958); cf. W. H. T. Davison and G. R. Bates, *J. Chem. Soc.* 2607 (1953)]. However all such compounds are substituted in the α-position by an oxygen function.

[24] L. Ruzicka, *Experientia* **9**, 357 (1953).
[25] G. S. Krishna Rao, Sukh Dev and P. C. Guha, *J. Ind. Chem. Soc.* **29**, 589 (1952).
[26] J. T. Arnold and M. E. Packard, *J. Chem. Phys.* **19**, 1608 (1951).
[27] J. R. Zimmerman and M. R. Foster, *J. Phys. Chem.* **61**, 282 (1957).

Tetrahedron, 1960, Vol. 9, pp. 10 to 28. Pergamon Press Ltd. Printed in Northern Ireland

# THE APPLICATION OF THE HAMMETT EQUATION TO THE THEORY OF TAUTOMERIC EQUILIBRIUM

## THIONE–THIOL EQUILIBRIUM, ACIDITY, AND STRUCTURE OF PHOSPHORUS THIO-ACIDS*†

M. I. KABACHNIK, T. A. MASTRUKOVA, A. E. SHIPOV and T. A. MELENTYEVA
Institute of Organo-Element Compounds, U.S.S.R. Academy of Sciences

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**Abstract**—The applicability of the Hammett equation to the effective ionization constants of tautomeric substances has been investigated. The tautomeric equilibrium being shifted toward one of the forms, a good linear dependence of $pK_A$ on $\sigma$ is observed. When at particular $\sigma$ values the second tautomeric form makes its appearance in the equilibrium to a noticeable extent one observes the deviation from linearity. It is seen to run parallel to the increase of that form in the equilibrium. The tautomeric equilibrium constant is related to the deviations form linearity '$a$' by a simple correlation $K_T = K_1/K_2 = 10^a - 1$ Thus has been established the quantitative relationship between the ionization constants of particular forms, the effective ionization constants of tautomeric substances and the $\sigma$ values.

The relationships determined were used to investigate the thione–thiol tautomerism of thio-organo-phosphorus compounds. To this end the Hammett equation has been previously shown to be applicable to organo-phosphorus acids of the type RR'P(O)OH and RR'P(*S*)*SH* and the $\sigma$ constants, characteristic of phosphorus compounds, have been determined. 25 phosphorus monothio- and 16 dithio-acids were synthesized, their ionization constants determined in aqueous 7 per cent and 80 per cent alcohol and the tautomeric equilibrium constants evaluated. For most phosphorus thio-acids the equilibrium has been shown to be shifted toward the thione form RR'P(S)OH, the second, or thiol form RR'P(O)SH appearing in noticeable amounts only with such substituents whose $\sigma$ value is near to 0. This effect is stronger in the 7 per cent than in the 80 per cent alcohol.

### 1. *General considerations*

AN important place is occupied in the theory of isomeric equilibrium or tautomerism by the dependence of the equilibrium on the structure of isomeric forms, the media, and other factors. In our previous work it had been shown[1–11] that it is possible to obtain efficient results by applying to prototropic tautomerism the modern theory of

* Translated by A. L. Pumpiansky, Moscow.

† Read at the Jubilee Conference of the Hungarian Chemist Society 12, May 1958 in Budapest; *Acta Chim. Hung.* **18**, 407 (1959), and at the Mendeleev Congress, Moscow, 18 March 1959.

[1] M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **83**, 407 (1952).
[2] M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **83**, 859 (1952).
[3] M. I. Kabachnik and T. A. Mastrukova, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* 163 (1953).
[4] M. I. Kabachnik and S. T. Joffe, *Dokl. Akad. Nauk SSSR* **91**, 833 (1953).
[5] M. I. Kabachnik, *Proceedings of the Kiev Conference, June* 1952, p. 126. AN, U.S.S.R. (1954).
[6] M. I. Kabachnik, *Izv. Akad. Nauk SSSR* 98 (1955).
[7] M. I. Kabachnik, S. T. Joffe and T. A. Mastrukova, *Zh. Obshch. Khim.* **25**, 684 (1955).
[8] M. I. Kabachnik, N. I. Kurochkin, T. A. Mastrukova, S. T. Joffe, E. M. Popov and N. P. Rodionova, *Dokl. Akad. Nauk SSSR* **104**, 861 (1955).
[9] M. I. Kabachnik, *Usp. Khim. SSSR* **25**, 137 (1956).
[10] M. I. Kabachnik, S. T. Joffe and Yu. N. Sheinker, *Zh. Obshch. Khim.* **26**, 2025 (1956).
[11] M. I. Kabachnik, S. T. Joffe and K. V. Vatzuro, *Tetrahedron* **1**, 317 (1957).

acid–base equilibrium in solutions, as proposed by Brønsted[12] and later developed by other authors.[13]

The qualitative ionic theory of tautomerism due to Lapworth *et al.*[14–17] as well as to Arndt and Eistert,[18–20] starting from the concept of the formation of a "common ion" has been quantitatively interpreted.[1–11] By using the Brønsted equation[12] and the relationship*

$$K_{TS} = C_{2S}/C_{1S} = K_{1S}/K_{2S} = K_1/K_2 \cdot f_{1S}/f_{2S} \qquad \text{(I)}$$

it proved possible to elucidate the regularities concerning the effect of solvents on the tautomeric equilibrium constants, at least within the limitations of the acid–base equilibrium theory, as to the effect of the solvents on the strength of acids and bases.

In particular, it was shown that the logarithms of the tautomeric equilibrium constants in two different solvents are in a linear relationship[1]

$$\mathrm{p}K_{TS_1} = \mathrm{p}K_{TS_2} + \text{Const} \qquad \text{(II)}$$

This linear relationship proved valid not only for keto-enols that were the first to exemplify it, but for a number of other types of tautomeric systems as well, such as α-acylaminopyridines and α-acylaminothiazols,[21] derivatives of dithizone,[22] thiocarboxylic acids,[23] etc.

The application of the Brønsted equation to the solutions of tautomeric compounds enabled to work out a method to evaluate the tautomeric equilibrium constants in terms of the data obtained by measuring the effective ionization constants of tautomeric mixtures in two particular solvents.[4] This method has been, in particular, used by two of the authors and Joffe to evaluate the tautomeric equilibrium constants of dialkyl hydrogen thiophosphates in 7 per cent and 80 per cent alcohol.

It was thereby found that in the latter case the equilibrium is shifted toward the thione forms and in the former one toward the thiol forms. The equilibrium of alkyl hydrogen alkylthiophosphonates

*$K_{TS}$ is the tautomeric equilibrium constant; $K_{1S}$ and $K_{2S}$ are ionization constants; $K_1$ and $K_2$ are the thermodynamic constants of acidity, and $f_{1S}$ and $f_{2S}$ are the respective coefficients of activity in the medium $S$, taken in terms of a standard for all solvents; $C_{1S}$ and $C_{2S}$ are the concentrations of form (I) and (II) in the medium ($S$).

[12] Y. N. Brønsted, *Chem. Rev.* **5**, 291 (1928); *Z. Phys. Chem.* **A169**, 32 (1939).
[13] N. A. Izmailov, *Z. Phys. Khim.* **23**, 639, 643 (1949); **24**, 321 (1950)
[14] A. Lapworth and A. O. Hann, *J. Chem. Soc.* **81**, 1512 (1912).
[15] T. Lowry, *J. Chem. Soc.* 2557 (1927).
[16] C. Ingold, C. Shoppe and J. F. Thorpe, *J. Chem. Soc.* 1477 (1926).
[17] J. Baker, *Tautomerism.* Routledge, London (1934).
[18] F. Arndt and C. Martius, *Liebigs Ann.* **499**, 262 (1932).
[19] F. Arndt and B. Eistert, *Ber. Dtsch. Chem. Ges.* **74**, 423 (1941).
[20] F. Arndt, L. Loewe and R. Ginkök, *Rev. Fac. Sci. Univ. Istambul* **A11**, 1947 (1946).
[21] Yu. N. Sheinker, *Dokl. Akad. Nauk. SSSR* **113**, 5 (1957).
[22] P. S. Pelkis and R. G. Dubenko, *Ukrain Khim. Zh.* **23**, 748 (1957).
[23] S. T. Joffe, Yu. N. Sheinker and M. I. Kabachnik, *Izv. Akad. Nauk S.S.S.R.* In press.

was found to be shifted in both alcohol and water toward the thione forms.[8] Thus it has been proved that the thione-thiol equilibrium of phosphorus thioacids depends to a great extent both on the nature of the solvent and the structure of tautomeric acids, such a relationship being also characteristic of many other types of tautomerism. The effect of the solvent can be therby interpreted in terms of the Brønsted–Izmailov theory of acid–base equilibrium. As to the effect of the structure of tautomeric substances it has been up to now possible to consider it only qualitatively on the basis of the known laws of organic chemistry. At the same time it seemed of great interest to establish the quantitative relationship between the structure of the forms and the tautomeric equilibrium. The tautomeric equilibrium being determined by the ratio of the ionization constants of the forms, the question of the effect of the structure on the equilibrium is that of the effect of the structure on their acid–base properties. In its general case the latter point is rather involved, but in particular cases one can make use of the empirical Hammett equation,[24]

$$\log K/K^\circ = \rho\sigma, \quad \text{or} \quad pK = pK^\circ - \rho\sigma \tag{III, IV}$$

that is particularly well applicable to the *meta*- and *para*- substituted aromatic acids. This led us to conduct the investigation of thione–thiol tautomerism of organo thiophosphorus acids along two lines, namely to consider firstly the general case of applying the Hammett equation to the ionization constants of tautomeric mixtures and secondly the particular case of applying this equation to the ionization of phosphorus acids.

2. *The application of the Hammett equation to the ionization constants of tautomeric compounds*

The Hammett equation has been applied by different authors to the problems of tautomerism. Thus, for instance, Jaffe,[25] Willy and Meyer[26] evaluated the tautomeric equilibrium constants through ionization constants calculated following Hammett. It is to be noted that the Hammett formula, though usually valid as a statistical equation for many uniform compounds, may lead to noticeable errors when used to evaluate the constants of a particular substance. A more general application of the equation is suggested in a recently published paper by Jaffe and Gardner[27] who have concurrently with the present authors dealt with two intersecting Hammett straight lines characteristic of the tautomeric equilibrium. The former authors have considered this approach only as a particular case to be applied to the tautomeric equilibrium of substituted azobenzenes and limited it to the case when the ionization constants $K^\circ$ of unsubstituted forms are equal (the two nitrogen atoms being equivalent in azobenzene). Neither have they given the problem under investigation a quantitative treatment.

We believe that being applied to the problems of tautomerism the Hammett equation should receive a more general and exhaustive treatment, involving the quantitative aspect of this problem.

As the tautomeric forms (ketones and enols, thiones and thiols, etc.) refer to acids of different chemical types, the relationship between their p$K$'s and $\sigma$'s must be

[24] L. P. Hammett, *Physical Organic Chemistry*. McGraw-Hill, New York (1940).
[25] H. H. Jaffe, *J. Amer. Chem. Soc.* **77**, 4445 (1955).
[26] A. V. Willi and W. Meyer, *Helv. Chem. Acta* **39**, 54, 318 (1956).
[27] H. H. Jaffe and R. W. Gardner, *J. Amer. Chem. Soc.* **80**, 319 (1958).

expressed by different values of $pK^\circ$ and $\rho$. Thus for the tautomeric forms $1 \leftrightharpoons 11$ we must write

$$pK_1 = pK_1^\circ - \rho_1\sigma \tag{IVa}$$

and

$$pK_2 = pK_1^\circ - \rho_2\sigma \tag{IVb}$$

In the general case a plot of $pK$ vs. $\sigma$ should be expressed by two intersecting straight lines (1) and (2), see Fig. 1, each of which expresses the relationship between $pK$ and $\sigma$ for one type of forms. The tautomeric equilibrium constant being equal to the ionization constants ratio of the forms in a given medium and hence

$$pK_T = pK_1 - pK_2 \tag{V}$$

it must be calculated for each substance (for each $\sigma$ value) by the intercept "$C$" of the ordinate between the two straight lines. The intersection point of the straight lines refers to that substituent which results in the tautomeric equilibrium constant being equal to unity. The region to the left from this point corresponds to the equilibrium shift toward form (1), that to the right toward form (11). In all cases the equilibrium is shifted to the forms corresponding to the above lying rays of straight lines. Thus if $\rho_1$ and $\rho_2$, and, respectively, $pK_1^\circ$ and $pK_2^\circ$ are known, it is possible to obtain a complete picture of the effect of the structure (the nature of the substituent, and the $\sigma$ value) on the tautomeric equilibrium and acidity of tautomeric forms.

In most cases, however, the direct experimental determination of ionization constants of single forms proved to be impossible. The attempted determination by Schwarzenbach and Lutz[28] using an extremely precise flowing potentiometric procedure met with failure.

Actually when determining the ionization constants of tautomeric compounds one determines some effective ionization constant related to the ionization constants of single forms by the equation (VI).[2]

$$K_a = K_1K_2/K_1 + K_2 \tag{VI}$$

It is thereby to be noted that if $K_2 \gg K_1$ then $K_a \cong K_1$, and if $K_2 \ll K_1$ then $K_a \cong K_2$.

The effective constant is always close to the ionization constant of that form which under given conditions is less acidic. With $pK$ and $\sigma$ the relationship between effective constant $K_a$ and $\sigma$ is expressed by a curve with two asymptotes overlapping with two above lying rays of the straight lines. Analytically it can be expressed through equation (VII) derived from (VI) by substituting $K_1$ and $K_2$, taken from equations (IVa) and (IVb)

$$K_a = \frac{K_1^\circ \cdot 10^{\rho_1\sigma} \cdot K_2^\circ \cdot 10^{\rho_2\sigma}}{K_1^\circ \cdot 10^{\rho_1\sigma} + K_2^\circ \cdot 10^{\rho_2\sigma}} \tag{VII}$$

This curve passes above the intersection point of two straight lines at a distance equal to log 2*.

One can suggest therefrom two ways of determining the tautomeric equilibrium constants on the basis of experimental determination of effective ionization constants

* The formula, suggested by Jaffé and Gardner is derived from VII at $K^\circ = K_1^\circ = K_2^\circ$ that is to say, it is applicable to the particular case when the ionization constants of two unsubstituted tautomeric forms are equivalent (at $\sigma = 0$).

[28] G. Schwarzenbach and K. Lutz, *Helv. Chem. Acta* **23**, 1147 (1940).

$K_a$ of various uniform tautomeric mixtures differing as to the nature and position of substituents (that is, in the magnitude of $\sigma$'s).

The first is used to evaluate the ionization constants of two sets of compounds, whose substituents cause the tautomeric equilibrium shift practically entirely either to the form 1 or to the form 2, respectively. The plot of p$K$ vs. $\sigma$ leads to two intercepts of above lying rays of intersecting straight lines at some distance from the point of intersection. Extrapolating to the middle one obtains two intersecting lines characteristic of the tautomeric equilibrium depending on $\sigma$. Investigations have shown the

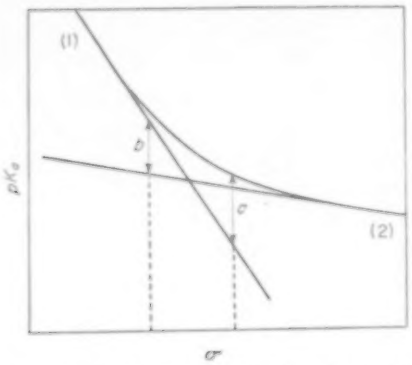


FIG. 1. A plot of p$K_a$ vs. $\sigma$ for tautomeric compounds.

application of this treatment to be limited to those rare cases when the nature of the substituent exerts such a strong influence on the equilibrium that it is possible to obtain experimental points corresponding to both rays.

As to the second way of determining the tautomeric equilibrium constants used in this paper, it is enough to have one ray and the region of deviation from it. Indeed from formula (VI) we obtain

$$pK_a - pK_1 = \log (K_1 + K_2) - \log K_2 \qquad \text{(VIII)}$$

or else, taking into account formula (1),

$$pK_a - pK_1 = \log (K_T + 1) \qquad \text{(IX)}$$

The $pK_a - pK_1$ being the ordinate deviation of the experimental curve from the linear relationship or the intercepts $a$ (Fig. 1), one finally obtains:

$$K_T = 10^a - 1 \qquad \text{(X)}$$

Thus, the intercept of the straight line and the deviations from its extension obtained experimentally enable one to reproduce the two intersecting straight lines, that is the whole picture of the relationship between the tautomeric equilibrium constants or the ionization constants of particular forms and $\sigma$.

Practically, the investigation proceed as follows. The effective ionization constants of tautomeric mixtures of various uniform compounds differing in the nature of substituents (or the magnitudes of $\sigma$) are evaluated. According to the data obtained p$K$ is plotted against $\sigma$. If the plot gives a linear relationship it is concluded that for all compounds under study the tautomeric equilibrium is almost entirely shifted to one of the forms. But if the experimental data give rise to a curve with only one

branch showing the linear relationship and the other deviating from it, then the conclusion is drawn that firstly the equilibrium is shifted to one of the forms for the compounds corresponding to the linear part of the curve and secondly, in the region of deviation appears a second form in equilibrium. The intercepts $a$ enclosed between the curve and the straight line produced by extrapolating the linear part of the curve are characteristic of the tautomeric equilibrium constant according to equation (X).

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### 3. *The application of the Hammett equation to organophosphorus compounds*

Jaffe *et al.*[29] have shown the Hammett equation to be applicable to the constants of the first and second ionization steps of aromatic phosphonic acids whose benzene ring involves a system transmitting the substituent effect to the reaction centre $PO(OH)_2$.

As far as organophosphorus compounds are concerned it is however possible to apply the Hammett equation far more extensively. It is to be expected that the readily polarizable electronic sphera of P=O and P=S groups can well transmit the substituent effect to the reaction centre, say, to OH or SH groups of acids and thio acids of phosphorus, such as

no matter whether the aromatic rings are present or not. The large atomic radius of phosphorus provides for the lack of steric hindrance between atoms and atom groups bound to phosphorus or, in any case, minimizes them. Thus all conditions are met for the Hammett formula to be applied to such compounds, the P=O group playing hereby the part of the aromatic ring transferring the polar effects and the R and R′ groups bound to phosphorus producing the substituent effect. To prove this postulate we treated[30,31] the experimental data (partly obtained in our laboratory and partly taken from the literature) of the ionization constants of about 100 phosphorus acids in various solvents (water, 7 per cent, 50 per cent, and 80 per cent alcohol) that roughly gave rise to 200 ionization constants. Hypophosphorus acid ($R = R' = H$, $\sigma = 0$) was taken as reference acid. With other acids the R and R′ groups were H, OH, AlkO, ArO, Alk, and Ar with different substituents in the hydrocarbon radical and in various combinations. The constant $\rho$ was taken for the first ionization step in aqueous solution as unity. The calculation was carried out in terms of the formula $pK = pK^\circ - \rho\Sigma\sigma$ with $\Sigma\sigma$ being the sum of the $\sigma$ constants of R and R′ substituents. By successive approximation were calculated the $\sigma$ constants characteristic of each substituent and the values of $\rho$ and $pK^\circ$. The linear relationship $pK = pK^\circ - \rho\Sigma\sigma$ proved to hold in all cases, as is seen from Figs. 2–6. In Table 1 are listed the $\sigma$ constants obtained. It is natural that the $\sigma$ constants for organophosphorus compounds are different from those evaluated by Hammett and subsequent workers[32] for the substituents in the benzene ring. Table 2 lists the corresponding values of constants $\rho$, $pK^\circ$ and correlation coefficients $r$.

[29] H. H. Jaffe, L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.* **75**, 2209 (1953).
[30] M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **110**, 393 (1956).
[31] T. A. Mastrukova, A. E. Shipov, T. A. Melentyeva and M. I. Kabachnik, *Zh. Obshch. Khim.* **29**, 2178 (1959).
[32] H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

Considerable deviations from linear relationship are observed only with compounds containing the $CCl_3$ and $CF_3$ groups. Again, the $\sigma$ constant for $C_6H_5$ and $p$-$CH_3C_6H_4$ groups depends on the number of these groups bound to the phosphorus atom. With

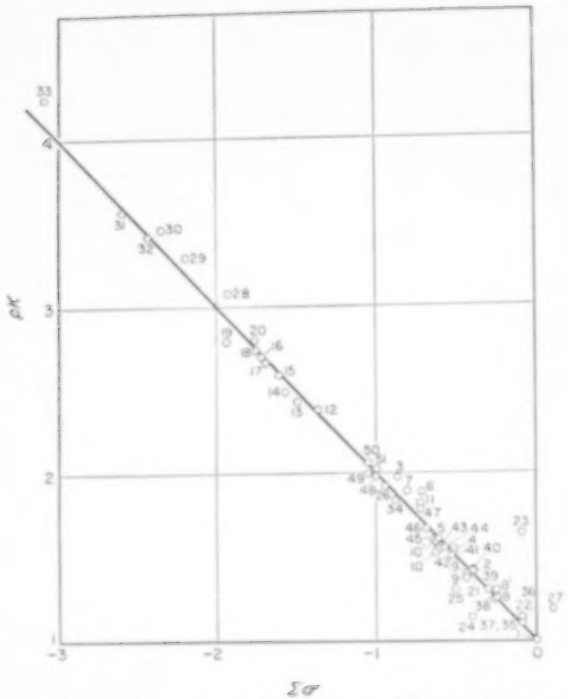


FIG. 2. Acids RR'P(O)OH in water, the first step $(pK_1)$[7-10,32-43] R and R': (1) H, H; (2) H,HO; (3) HO,HO; (4) $CH_3O$,HO; (5) $C_2H_5O$,HO; (6) $C_3H_7O$,HO; (7) $C_4H_9O$,HO; (8) $CH_3O$,$CH_3O$; (9) $C_2H_5O$, $C_2H_5O$*; (10) $C_3H_7O$, $C_3H_7O$*; (11) $C_4H_9O$, $C_4H_9O$; (12) $CH_3$,HO; (13) $C_2H_5$,HO; (14) $C_3H_7$,HO; (15) $C_4H_9$,HO; (16) i-$C_4H_9$,HO; (17) i-$C_3H_7$,HO; (18) s-$C_4H_9$,HO; (19) t-$C_4H_9$,HO; (20) $C_{12}H_{25}$,HO; (21) $ClCH_2$,HO; (22) $Cl_2CH$,HO; (23) $Cl_3C$,HO; (24) $BrCH_2$, HO; (25) $ICH_2$,HO; (26) $HOCH_2$,HO; (27) $F_3C$,HO; (28) $CH_3$,$CH_3$; (29) $C_2H_5$,$C_2H_5$; (30) $C_3H_7$,$C_3H_7$; (31) i-$C_3H_7$,i-$C_3H_7$; (32) $C_4H_9$,$C_4H_9$; (33) t-$C_4H_9$,-$C_4tH_9$, (34) $C_6H_5$,HO; (35) $m$-$CH_3N^+H_2C_6H_4$,HO; (36) $p$-$(CH_3)_2N^+HC_6H_4$, HO; (37) $m$-$C_6H_5N^+H_2C_6H_4$,HO; (38) $p$-$NO_2C_6H_4$,HO; (39) $m$-$NO_2C_6H_4$,HO; (40) $p$-$NH_2SO_2C_6H_4$, HO; (41) $p$-$HOOCC_6H_4$,HO; (42) $m$-$BrC_6H_4$,HO; (43) $m$-$ClC_6H_4$,HO; (44) $m$-$HOOCC_6H_4$,HO; (45) $p$-$BrC_6H_4$,HO; (46) $p$-$ClC_6H_4$,HO; (47) $m$-$HOC_6H_4$,HO; (48) $p$-$CH_3C_6H_4$,HO; (49) $p$-$HOC_6H_4$,HO; (50) $p$-$C_2H_5OC_6H_4$,HO; (51) $p$-$CH_3OC_6H_4$,HO.

* Data obtained in 7 per cent alcohol.

one aromatic group the $\sigma$ values amount to $-0{\cdot}481 \pm 0{\cdot}020$ and $-0{\cdot}602 \pm 0{\cdot}010$ and with two groups $-0{\cdot}592 \pm 0{\cdot}017$ and $-0{\cdot}674 \pm 0{\cdot}016$, respectively. This seems to be due to steric hindrance.

We have also investigated the relationship between p$K$ and $\Sigma\sigma$ for dithio-acids of phosphorus such as

The data obtained are summarized in Fig. 7. The ionization constants of the acids of

the dithio series proved to be little dependent on the nature of the radicals R and R′. In 7 per cent and 80 per cent alcohol, $\rho$ amounts to 0·007 and −0·022 respectively, $pK^\circ$ being 1·74 and 2·64.

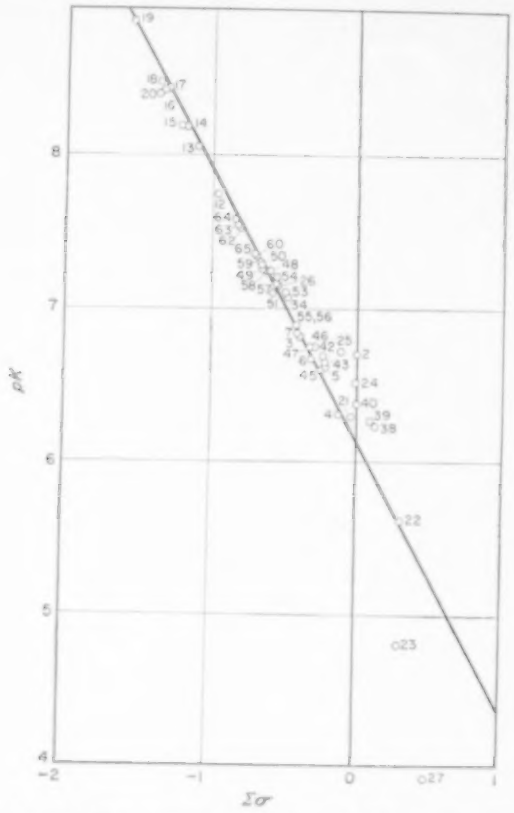


FIG. 3. Acids RR′P(O)OH in water; the second step ($pK_2$)[30,33–41] R and R′: denominations as in Fig. 2 and in addition: (53) $p$-$CH_3CONHC_6H_4.HO$; (54) 3,4-$CH_2O_2C_6H_3.HO$; (55) $p$-$^-OOCC_6H_4.HO$; (56) $m$-$^-OOCC_6H_4.HO$; (57) $m$-$NH_2C_6H_4.HO$; (58) $m$-$C_2H_5NHC_6H_4.HO$; (59) $m$-$CH_3NHC_6H_4.HO$; (60) $m$-$C_4H_9NHC_6H_4.HO$; (62) $p$-$NH_2C_6H_4.HO$; (63) $p$-$NH_2NHC_6H_4.HO$; (64) $p$-$CH_3NHC_6H_4.HO$; (65) $p$-$(CH_3)_2NC_6H_4.HO$.

## 4. *Phosphorus thio-acids. Synthetic methods and ionization constants*

To proceed to the investigation we synthesized 25 phosphorus monothio-acids involving derivatives of thiophosphoric, alkylthiophosphonic and dialkyl- (diaryl) thiophosphinic acids, mostly not described in the literature. To this end we have

[30] H. H. Jaffe, *Chem. Rev.* **53**, 191 (1953).
[33] A. C. Mitchell, *J. Chem. Soc.* **117**, 957 (1920).
[35] F. W. Bennett, H. J. Emeléus and R. N. Haszeldine, *J. Chem. Soc.* 3598 (1954).
[36] W. D. Kumler and J. J. Eiler, *J. Amer. Chem. Soc.* **65**, 2355 (1943).
[37] P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.* **75**, 3379 (1953).
[38] P. Rumpf and V. Chavane, *C.R. Acad. Sci., Paris* **224**, 919 (1947).
[39] P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.* **75**, 5738 (1953).
[40] H. J. Emeléus, R. N. Haszeldine and R. C. Paul, *J. Chem. Soc.* 563 (1955).
[41] H. H. Jaffe, L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.* **75**, 2209 (1953).
[42] P. Lesfauries and P. Rumpf, *C.R. Acad. Sci., Paris* **228**, 1018 (1949).

elaborated some general synthetic procedures that enabled us to obtain different acids in good and fair yields in a pure state.

Dialkyl thiophosphates $(RO)_2PSOH$ were obtained by treating triethylammonium dialkyl thiophosphates with mineral acids, the former being, in turn, synthesized by

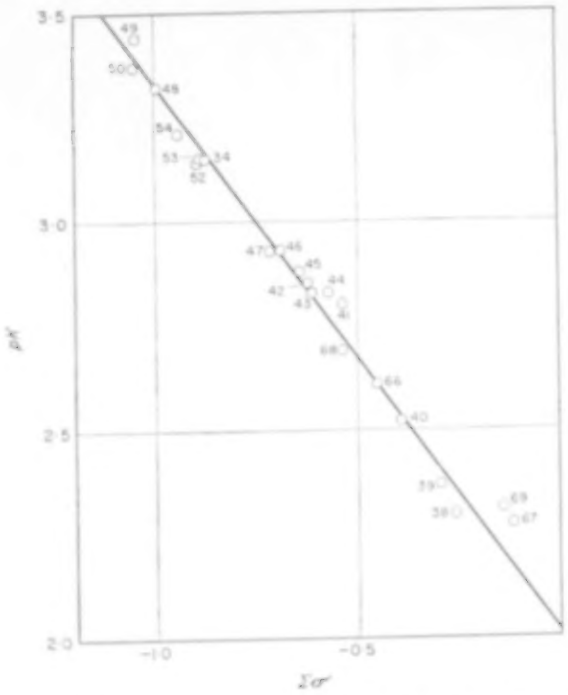


FIG. 4. Acids RR'P(O)OH *in* 50 per cent alcohol; the first step $(pK_1)^{38,39-41}$ R and R': Denominations as in Figs. 2 and 3 and in addition: (66) $C_6H_5O,HO$; (67) $C_6H_5O$, $C_6H_5O$; (68) $p$-$CH_3C_6H_4O,HO$; (69) $p$-$CH_3C_6H_4O$, $p$-$CH_3C_6H_4O$.

the sulphur addition to dialkyl hydrogen phosphites in the presence of triethylamine as follows:

$$(RO)_2PHO \xrightarrow[(C_2H_5)_3N+S]{} (RO)_2PSONH(C_2H_5)_3 \xrightarrow[HCl]{} (RO)_2PSOH \qquad \text{(Method A)}$$

We also used the route via sodium dialkyl thiophosphates following Arbuzov[43] and Foss[44]:

$$(RO)_2PHO \xrightarrow[Na]{} (RO)_2PONa \xrightarrow[S]{} (RO)_2PSONa \xrightarrow[HCl]{} (RO)_2PSOH \qquad \text{(Method B)}$$

Diphenyl thiophosphoric acid was produced as triethylammonium salt from diphenyl chlorophosphate, hydrogen sulphide, and triethylamine:

$$(ArO)_2POCl \xrightarrow[H_2S+(C_2H_5)_3N]{} (ArO)_2PSONH(C_2H_5)_3 \qquad \text{(Method C)}$$

Alkyl hydrogen alkylthiophosphonates RPS(OR)(OH), were prepared via two routes.

[43] A. E. Arbuzov, *VIth Mendelew Congress Abstracts* Part 11, p. 124. Kharkov (1932).
[44] O. Foss, *Acta Chem. Scand.* **1**, 8 (1947).

1. From dialkyl hydrogen thiophosphites according to the following scheme:

$$(RO)_2PHS \xrightarrow[Na]{} (RO)_2PSNa \xrightarrow[R'X]{} R'PS(OR)_2 \xrightarrow[NaOH]{} R'PS(OR)(ONa) \xrightarrow[HCl]{} R'PS(OR)(OH)$$

(Method D)

2. From alkyl hydrogen alkylphosphonous acids:

$$R'P(OR)HO \xrightarrow[Na]{} R'P(OR)(ONa) \xrightarrow[S]{} R'PS(OR)ONa \xrightarrow[HCl]{} R'PS(OR)(OH)$$

(Method E)

Diarylthiophosphinic acids, $Ar_2PSOH$, were produced following the known procedure due to Higgins *et al.*[45] (Method F). To obtain dialkylthiophosphinic acids,

FIG. 5. Acids R-PO(OH)$_2$ in 50 per cent alcohol; the second step (p$K'_2$)[50,58–61] R: Denominations as in Figs. 2, 3 and 4 and in addition: (70) $C_6H_5O$; (71) *p*-$CH_3C_6H_4O$.

$R_2PSOH$, we made use of the Kosolapoff reaction[46] of dialkyl hydrogen phosphites with organo-magnesium compounds. The magnesium salts produced thereby are found readily to add sulphur to give magnesium dialkylthiophosphinates.[47] The general synthetic scheme is as follows:

$$(RO)_2PHO \xrightarrow{R'MgX} R_2'POMgX \xrightarrow{S} R_2'PS(OMgX) \xrightarrow[HCl]{} R_2'PSOH$$

(Method G)

An exception proved to be di-t-butylthiophosphinate, that we succeeded in obtaining by substituting t-butyllithium for t-butylmagnesium chloride.

The data concerning phosphorus thio-acids produced are given in Table 3.

[45] W. A. Higgins, P. W. Vogel and W. G. Craig, *J. Amer. Chem. Soc.* **77**, 1864 (1955).
[46] G. M. Kosolapoff and R. M. Watson, *J. Amer. Chem. Soc.* **73**, 4101 (1951).
[47] T. A. Mastrukova, A. E. Shipov and M. I. Kabachnik, *Zh. Obsch. Khim.* **29**, 1450 (1959).

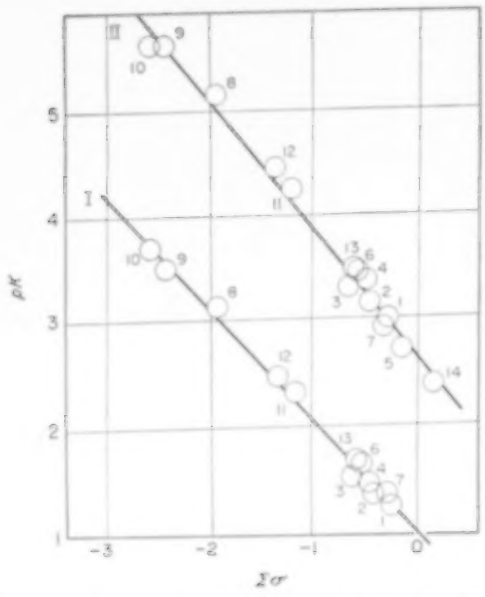


FIG. 6. Acids RR'P (O)OH in 7 per cent alcohol and 80 per cent alcohol at 20°. The first step ($pK_1$). R and R': (1) $CH_3O$, $CH_3O$; (2) $C_2H_5O$, $C_2H_5O$; (3) $C_3H_7O$, $C_3H_7O$; (4) $C_6H_5O$, HO; (5) $C_6H_5O$, $C_6H_5O$; (6) $p$-$CH_3C_6H_4O$,HO; (7) $p$-$CH_3C_6H_4O$, $p$-$CH_3C_6H_4O$; (8) $CH_3O$, $CH_3$; (9) $C_3H_9$, $C_4H_9$; (10) i-$C_4H_9$, i-$C_4H_9$; (11) $C_6H_5$,$C_6H_5$; (12) $p$-$CH_3C_6H_4$, $p$-$CH_3C_6H_4$; (13) $p$-$ClC_6H_4$, $p$-$ClC_6H_4$; (14) $m$-$NO_2C_6H_4$, $m$-$NO_2C_6H_4$.

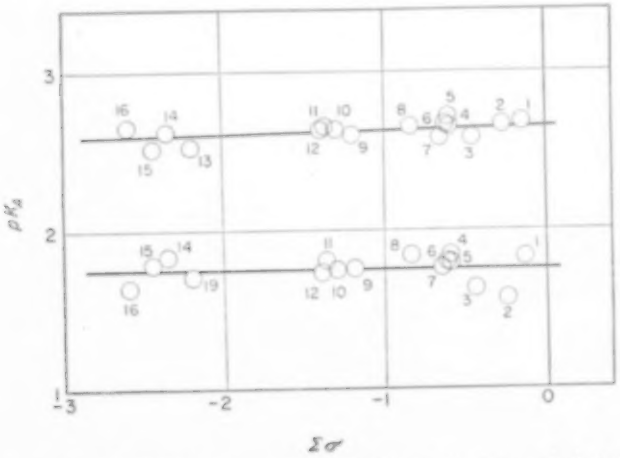


FIG. 7. Acids RR'P(S)SH in 7 per cent alcohol (1) and 80 per cent alcohol (2) at 20°. The first step ($pK_1$). R and R': (1) $C_6H_5O$, $C_6H_5O$; (2) $CH_3O$,$CH_3O$; (3) $C_6H_5O$,$C_2H_5O$; (4) i-$C_3H_7O$; i-$C_3H_7O$; (5) $p$-$ClC_6H_4$, $p$-$ClC_6H_4$; (6) i-$C_4H_9O$, i-$C_4H_9O$; (7) $C_3H_7O$,$C_3H_7O$; (8) $C_4H_9O$, $C_4H_9O$; (9) $C_6H_5$,$C_6H_5$; (10) $CH_3$,$C_5H_{11}O$; (11) $p$-$CH_3C_6H_4$, $p$-$CH_3C_6H_4$; (12) $CH_3$,$C_4H_9O$; (13) $C_2H_5$,$C_2H_5$; (14) $C_3H_7$, $C_3H_7$; (15) $C_4H_9$,$C_4H_9$, (16) i-$C_3H_7$, i-$C_3H_7$.

TABLE 1. THE CONSTANTS OF SUBSTITUENTS $\sigma$[20,21]

| R | $\sigma$ | $\pm\Delta\sigma$ | R | $\sigma$ | $\pm\Delta\sigma$ |
|---|---|---|---|---|---|
| H | 0 | | *m*-$CH_3N^+H_2C_6H_4$ | 0·30 | |
| HO | −0·393 | 0·007 | *p*-$(CH_3)_2N^+HC_6H_4$ | 0·30 | |
| $CH_3O$ | −0·124 | 0·014 | *m*-$C_5H_5N^+H_2C_6H_4$ | 0·30 | |
| $C_2H_5O$ | −0·214 | 0·014 | *p*-$NO_2C_6H_4$ | 0·132 | 0·045 |
| $C_3H_7O$ | −0·315 | 0·048 | *m*-$NO_2C_6H_4$ | 0·096 | 0·041 |
| i-$C_3H_7O$ | −0·291 | 0·004 | *p*-$NH_2SO_2C_6H_4$ | 0·000 | 0·039 |
| $C_4H_9O$ | −0·411 | 0·043 | *p*-$HOOCC_6H_4$ | −0·140 | 0·040 |
| i-$C_4H_9O$ | −0·300 | 0·000 | *m*-$HOOCC_6H_4$ | −0·177 | 0·027 |
| $C_6H_5O$ | −0·061 | 0·012 | *m*-$ClC_6H_4$ | −0·219 | 0·024 |
| *p*-$CH_3C_6H_4O$ | −0·141 | 0·011 | *m*-$BrC_6H_4$ | −0·229 | 0·028 |
| $CH_3$ | −0·965 | 0·023 | *p*-$BrC_6H_4$ | −0·248 | 0·015 |
| $C_2H_5$ | −1·101 | 0·020 | *p*-$ClC_6H_4$ | −0·292 | 0·014 |
| $C_3H_7$ | −1·177 | 0·025 | *m*-$HOC_6H_4$ | −0·322 | 0·022 |
| i-$C_3H_7$ | −1·300 | 0·036 | *p*-$^-OOCC_6H_4$ | −0·418 | 0·008 |
| $C_4H_9$ | −1·219 | 0·015 | *m*-$^-OOCC_6H_4$ | −0·418 | 0·008 |
| i-$C_4H_9$ | −1·297 | 0·010 | *m*-$HN_2NHC_6H_4$ | −0·465 | |
| s-$C_4H_9$ | −1·363 | 0·023 | $C_6H_5$ | −0·481 | 0·020 |
| t-$C_4H_9$ | −1·546 | 0·098 | $C_6H_5$* | −0·592 | 0·017 |
| $C_{12}H_{25}$ | −1·369 | 0·031 | *p*-$CH_3CONHC_6H_4$ | −0·493 | 0·028 |
| $ClCH_2$ | −0·034 | 0·034 | *p*-$C_2H_5SC_6H_4$ | −0·500 | 0·045 |
| $Cl_2CH$ | 0·272 | 0·019 | 3,4-$CH_2O_2C_6H_3$ | −0·549 | 0·018 |
| $Cl_3C$ | 0·30 | 0·53 | *m*-$NH_2C_6H_4$ | −0·563 | 0·026 |
| $BrCH_2$ | −0·01 | 0·27 | *p*-$CH_3OC_6H_4$ | −0·586 | 0·034 |
| $HOCH_2$ | −0·546 | 0·036 | *p*-$CH_3C_6H_4$ | −0·602 | 0·010 |
| $F_3C$ | −0·50 | 0·27 | *p*-$CH_2C_6H_4$* | −0·674 | 0·016 |
| $^-O$ | 0 | | *m*-$C_2H_5NHC_6H_4$ | −0·621 | |
| | | | *p*-$HOC_6H_4$ | −0·652 | 0·017 |
| | | | *m*-$CH_3NHC_6H_4$ | −0·654 | |
| | | | *p*-$C_2H_5OC_6H_4$ | −0·658 | 0·005 |
| | | | *m*-$C_4H_9NHC_6H_4$ | −0·671 | |
| | | | *p*-$(CH_3)_2NC_6H_4$ | −0·682 | |
| | | | *p*-$NH_2C_6H_4$ | −0·783 | |
| | | | *p*-$NH_2NHC_6H_4$ | −0·789 | |
| | | | *p*-$CH_3NHC_6H_4$ | −0·811 | |

* With two phenyl or *p*-tolyl groups at the phosphorus atom.

TABLE 2. THE REACTIONS CONSTANTS $\rho$ AND THE VALUES OF $pK^\circ$ AND $r$ FOR THE IONIZATION OF ACIDS $RR'PO(OH)$ AND $RPO(OH)_2$

| Solvent | Ionization step | $n$ | $pK^\circ$ | $\rho$ | $r$ |
|---|---|---|---|---|---|
| Water | $K_1$ | 58 | 1·00 | 0·990 (1·000) | 0·976 |
| Water | $K_2$ | 47 | 6·13 | 1·788 | 0·955 |
| 7% alcohol | $K_1$ | 12 | 1·01 | 1·050 | 0·996 |
| 50% alcohol | $K_1$ | 17 | 2·01 | 1·312 | 0·993 |
| 50% alcohol | $K_2$ | 19 | 7·59 | 1·358 | 0·992 |
| 80% alcohol | $K_1$ | 14 | 2·68 | 1·219 | 0·994 |

TABLE 3. PHOSPHORUS THIO-ACIDS RR'PSOH AND RR'POSH

| No. | R | R' | B.p. | | M.p. °C | Synthetic method | Yield | $n_D^{20}$ | $d_4^{20}$ | Neutralization equivalent | | Analyses | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | °C | Pmm | | | | | | | | % C | | % H | | % P | |
| | | | | | | | | | | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. |
| 1. | $C_6H_5O$ | $C_6H_5O$[a] | — | — | 86–87 | C | 78 | — | — | — | — | 58·8<br>58·8 | 58·8 | 7·1<br>7·1 | 7·1 | 8·4<br>8·3 | 8·4 |
| 2. | $CH_3O$ | $CH_3O$[b] | — | — | 156 dec. | B | 67 | — | — | — | — | — | — | — | — | 18·7<br>18·8 | 18·9 |
| 3. | $C_2H_5O$ | $C_2H_5O$ | 106–107 | 2·5 | — | A,B | 54·60 | 1·4719 | 1·1806 | 168·5<br>167·0 | 170·2 | 28·3<br>28·4 | 28·2 | 6·6<br>6·7 | 6·5 | — | — |
| 4. | i-$C_3H_7O$ | i-$C_3H_7O$ | 89–90 | 1·5 | — | A | 72 | 1·4592 | 1·0906 | 198·5<br>197·6 | 198·2 | 36·3<br>36·7 | 36·4 | 7·6<br>7·5 | 7·6 | 15·4<br>15·8 | 15·6 |
| 5. | p-$ClC_6H_4$ | p-$ClC_6H_4$ | — | — | 103–104 | F | 77 | — | — | 303·5<br>303·9 | 303·2 | — | — | — | — | 10·4<br>10·4 | 10·2 |
| 6. | iso-$C_4H_9O$ | i-$C_4H_9O$ | 82·5–84 | 0·05 | — | A | 68 | 1·4570 | 1·0386 | 227·5<br>228·3 | 226·3 | 42·6<br>42·7 | 42·5 | 8·3<br>8·3 | 8·4 | 13·6<br>13·7 | 13·7 |
| 7. | $C_5H_7O$ | $C_5H_7O$ | 108·5–109·5 | 0·09 | — | A | 62 | 1·4678 | 1·1023 | 199·6<br>198·7 | 198·2 | 36·2<br>36·6 | 36·4 | 7·8<br>7·9 | 7·6 | 15·8<br>15·6 | 15·6 |
| 8. | $C_4H_9O$ | $C_4H_9O$ | 88–89 | 0·08 | — | A,B | 77·70 | 1·4654 | 1·0672 | 228·5<br>229·1 | 226·3 | 42·4<br>42·3 | 42·5 | 8·4<br>8·2 | 8·4 | 13·6<br>13·6 | 13·7 |
| 9. | $CH_3$ | $C_2H_5O$ | 72·5 | 1 | — | D | 53 | 1·4927 | 1·0800 | 136·4<br>140·3 | 140·2 | 25·6<br>25·6 | 25·7 | 6·5<br>6·5 | 6·5 | 21·8<br>21·8 | 22·1 |
| 10. | $C_6H_5$ | $C_6H_5$ | — | — | 141–142 | F | 79 | — | — | 234·3<br>234·1 | 234·3 | 61·4<br>61·6 | 61·5 | 4·5<br>4·7 | 4·7 | 13·0<br>13·1 | 13·2 |
| 11. | $CH_3$ | i-$C_3H_9O$ | 112–112·5 | 0·5 | — | D | 60 | 1·4819 | 1·0824 | 168·1<br>168·3 | 168·2 | 36·0<br>36·0 | 35·7 | 7·9<br>7·9 | 7·8 | 18·1<br>18·3 | 18·4 |
| 12. | $CH_3$ | $C_3H_7O$ | 106–107 | 2·5 | — | D | 62 | 1·4883 | 1·1293 | 154·0<br>154·3 | 154·2 | 31·3<br>31·4 | 31·2 | 7·2<br>7·2 | 7·1 | — | — |
| 13. | $C_2H_5$ | $C_2H_5O$ | 84·5–85·5 | 2 | — | D,E | 65 | 1·4916 | 1·1337 | 154·2<br>154·0 | 154·2 | 31·0<br>31·0 | 31·2 | 7·2<br>7·2 | 7·1 | 20·0<br>19·7 | 20·1 |
| 14. | $CH_3$ | $C_4H_9O$ | 90 | 0·5 | — | D | 60 | 1·4891 | 1·0993 | 169·7<br>168·2 | 168·2 | 35·6<br>35·4 | 35·7 | 7·8<br>7·9 | 7·8 | 18·1<br>18·2 | 18·4 |

TABLE 3 (*contd.*)

| No. | R | R' | B.p. °C | B.p. Pmm | M.p. °C | Synthetic method | Yield | $n_D^{20}$ | $d_4^{20}$ | Neutralization equivalent Found | Neutralization equivalent Calc. | Analyses %C Found | %C Calc. | %H Found | %H Calc. | %P Found | %P Calc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15. | $C_3H_7$ | $C_2H_5O$ | 101–102 | 2 | — | D | 33 | 1·4875 | 1·0974 | 165·0<br>166·8 | 168·2 | 36·1<br>36·0 | 35·7 | 8·0<br>7·8 | 7·8 | 18·5<br>18·6 | 18·4 |
| 16. | $C_4H_9$ | $C_2H_5O$ | 64·5–65 | 0·015 | — | D | 45 | 1·4831 | 1·0721 | 181·9<br>182·9 | 182·2 | 39·3<br>39·2 | 39·5 | 8·3<br>8·4 | 8·3 | 16·5<br>16·8 | 17·0 |
| 17. | $C_2H_5$ | $C_4H_9O$ | 110 | 1 | — | E | 74 | 1·4873 | 1·0810 | 182·9<br>181·5 | 182·3 | 39·8<br>39·6 | 39·6 | 8·3<br>8·5 | 8·3 | 16·7<br>17·0 | 17·0 |
| 18. | i-$C_4H_9$ | $C_4H_9O$ | 82 | 0·1 | — | E | 70 | 1·4821 | 1·0321 | 209·7<br>209·8 | 210·3 | 45·8<br>46·0 | 45·7 | 9·1<br>9·0 | 9·0 | 14·6<br>14·4 | 14·7 |
| 19. | $C_2H_5$ | $C_2H_5$ | 88·5–89 | 1·5 | 11·5 | G | 69 | 1·5262 | 1·1090 | 138·1<br>138·0 | 138·2 | 34·6<br>34·5 | 34·8 | 7·6<br>7·9 | 8·0 | 22·4<br>22·1 | 22·4 |
| 20. | $C_3H_7$ | $C_3H_7$ | 98·5–99 | 2 | 31 | G | 81 | — | — | 166·3<br>166·0 | 166·2 | 43·4<br>43·5 | 43·4 | 9·4<br>9·4 | 9·1 | 18·7<br>18·9 | 18·6 |
| 21. | $C_4H_9$ | $C_4H_9$ | 81–81·5 | 0·25 | *c* | G | 74 | — | — | 193·9<br>193·9 | 193·3 | 49·4<br>49·2 | 49·4 | 9·8<br>10·0 | 9·9 | 16·0<br>16·2 | 15·9 |
| 22. | i-$C_4H_9$ | i-$C_4H_9$ | — | — | 69·5–70·5 | G | 69 | — | — | 194·2<br>194·4 | 194·3 | 49·4<br>49·5 | 49·4 | 9·8<br>9·8 | 9·9 | 16·3<br>16·2 | 15·9 |
| 23. | i-$C_3H_7$ | i-$C_3H_7$ | — | — | 76–77·5 | G | 64 | — | — | 166·2<br>166·3 | 166·2 | 43·6<br>43·6 | 43·4 | 9·1<br>9·2 | 9·1 | — | — |
| 24. | s-$C_4H_9$ | s-$C_4H_9$ | 102–102·5 | 0·8 | 55·5–57 | G | 45 | — | — | 194·7<br>193·3 | 194·3 | 49·6<br>49·6 | 49·4 | 9·9<br>9·6 | 9·9 | 15,8<br>15·9 | 15·9 |
| 25. | t-$C_4H_9$ | t-$C_4H_9$ | — | — | 144–5 | G | 23 | — | — | 191·7<br>194·4 | 194·3 | 49·8<br>49·5 | 49·4 | 9·8<br>9·8 | 9·9 | 15·6<br>15·8 | 15·9 |

[a] Sodium salt. [b] Triethylammonium salt. [c] M.P. Not determined, the acid being extremely hygroscopic.

Dialkyl dithiophosphoric acids, $(RO)_2PSSH$, were obtained following Carius and Pishchimuka[48–51].

Alkyl hydrogen alkyldithiophosphonates, RPS(OR')SH, were produced by treating alkyl alkylchlorothiophosphonates with sodium hydrosulphide[52] as follows

$$R'PS(OR)Cl + NaSH \longrightarrow R'PS(OR)SNa \longrightarrow R'PS(OR)SH$$

Diaryldithiophosphinic acids, $Ar_2PSSH$, were obtained following Higgins *et al.*[45]

Dialkyldithiophosphinic acids were produced from dialkylthiophosphinic acids according to the scheme[53]:

$$R_2PSOH \xrightarrow[PCl_5]{} R_2PSCl \xrightarrow[NaSH]{} R_2PSSNa \xrightarrow[HCl]{} R_2PSSH.$$

In Table 4 are summarized the dithio-acids synthesized, their constants, analyses and ionization constants.

All $pK_a$'s were evaluated by measuring the pH's of the partly neutralized solutions using a glass electrode (potentiometer Moskip LP-5, biphthalate buffer with pH=4·00, temperature 20°, acid concentration $5 \cdot 10^{-3}$). $K_a$ was calculated by the equation:

$$^{*}K_a = (H^+) \cdot \frac{(Na^+) + (H^+) - K_w/(H^+)}{M - [(Na^+) + (H^+) - K_w/(H^+)]}$$

within the experimental error of up to $\pm 0{\cdot}05$ p$K$.

In Table 5 are listed the results of the determination of ionization constants of phosphorus thio-acids in 7 per cent† and 80 per cent alcohol by weight.

*Results and discussion*

As seen from Table 5 the ionization constants of phosphorus monothio-acids contrary to those of dithio-acids are steadily increasing with increasing $\Sigma\sigma$. In Fig. 8 the $pK_a$ of phosphorus monothio-acids is plotted against $\Sigma\sigma$. Thus, for acids with $\Sigma\sigma < -1$ in 80 per cent alcohol one can see a good linear relationship. This region corresponds to acids whose tautomeric equilibrium has been shown to be shifted toward the thione form.[7,8]

The least squares treatment resulted in $pK_1^\circ = 2{\cdot}00$, $\rho_1 = 1{\cdot}329$ with the correlation coefficient, $r_1$ being 0·998. Where $\Sigma\sigma > -1$, one observes deviations from linearity, the greater the larger is the $\Sigma\sigma$. In 7 per cent alcohol the deviations start at lower values of $\Sigma\sigma$ so that only the points with $\Sigma\sigma < -2$ make the extrapolation reliable. Thereby $pK_1^\circ = 0{\cdot}69$, $\rho_1 = 0{\cdot}924$, and $r_1 = 0{\cdot}962$.

* $K_w$ for 80% alcohol may be estimated to be $10^{-15}$ to $10^{-16}$ and in any case $K_w < 10^{-14}$. $K_w/H < Na + H$ when measuring $K_a$ of acids of medium acidity ($pK_a$ 2–6). Therefore $K_w/H$ may be disregarded. The $K_a$ constants obtained in this work are apparent ionization constants. This is due to the use of glass electrodes for measurements in low aqueous media and the liquid connexion of chains, as well as concentrations instead of activities is known to lead to systematic errors. The deviations are nearly constant when concentrations are sufficiently low (ionin force i = 0·01) and conditions are strictly constant as is the case in this work.

† 7 per cent alcohol was used because some of the acids under investigation are not soluble in pure water.

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TABLE 4. PHOSPHORUS DITHIO-ACID RR'PSSH

| No. | R | R' | B.p. °C | B.p. mm | $n_D^{20}$ | $d_4^{20}$ | Neutralization equivalent Found | Neutralization equivalent Calc. | $\Sigma\sigma$ | pK 7% Alc. | pK 80% Alc. | Analyses %C Found | %C Calc. | %H Found | %H Calc. | %P Found | %P Calc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | $C_6H_5O$ | $C_6H_5O$ | m.p. 60–61 | | — | — | 281·9<br>282·2 | 282·2 | −0·122 | 1·81 | 2·66 | 51·0<br>50·9 | 51·1 | 3·9<br>3·8 | 3·9 | 11·0<br>10·8 | 11·0 |
| 2. | $CH_3O$ | $CH_3O$ | 56–57 | 4 | 1·5340 | 1·2869 | 157·6<br>158·4 | 158·1 | −0·248 | 1·55 | 2·64 | 15·0<br>14·9 | 15·2 | 4·4<br>4·4 | 4·5 | — | — |
| 3. | $C_2H_5O$ | $C_2H_5O$ | 77–78 | 4 | 1·5073 | 1·1651 | 185·3<br>186·1 | 186·2 | −0·428 | 1·62 | 2·56 | 25·8<br>25·9 | 25·8 | 6·1<br>6·1 | 5·9 | 16·5<br>16·7 | 16·7 |
| 4. | $i\text{-}C_3H_7O$ | $i\text{-}C_3H_7O$ | 71–72 | 3 | 1·4918 | 1·0911 | 214·3<br>213·8 | 214·3 | −0·582 | 1·82 | 2·65 | — | — | — | — | 14·4<br>14·5 | 14·5 |
| 5. | $p\text{-}ClC_6H_4$ | $p\text{-}ClC_6H_4$ | m.p. 82–83 | | — | — | 318·7<br>318·2 | 319·2 | −0·584 | 1·79 | 2·69 | [a] | | | | | |
| 6. | $i\text{-}C_4H_9O$ | $i\text{-}C_4H_9O$ | 77·5–78 | 1·5 | 1·4921 | 1·0620 | 242·0<br>242·3 | 242·3 | −0·600 | 1·79 | 2·65 | 20·0<br>19·9 | 19·8 | 3·6<br>3·7 | 3·7 | 12·6<br>12·7 | 12·8 |
| 7. | $C_3H_7O$ | $C_3H_7O$ | 85–86 | 3 | 1·4987 | 1·1040 | 213·5<br>213·3 | 214·3 | −0·630 | 1·75 | 2·57 | — | — | — | — | 14·4<br>14·4 | 14·5 |
| 8. | $C_4H_9O$ | $C_4H_9O$ | 99–99·5 | 2 | 1·4971 | 1·0722 | 242·3<br>242·0 | 242·3 | −0·822 | 1·83 | 2·64 | 19·7<br>19·6 | 19·8 | 3·6<br>3·6 | 3·7 | 12·6<br>12·8 | 12·8 |
| 9. | $C_6H_5$ | $C_6H_5$ | m.p. 56 | | — | — | 250·2<br>250·4 | 250·3 | −1·184 | 1·75 | 2·60 | 57·7<br>57·5 | 57·6 | 4·5<br>4·4 | 4·4 | 12·2<br>12·0 | 12·4 |
| 10. | $CH_3$ | $C_3H_7O$[a,f] | m.p. 62–63 | | — | — | 190·9[b]<br>191·2 | 192·2 | −1·280 | 1·74 | 2·63 | 24·8<br>24·9 | 25·0 | 5·3<br>5·1 | 5·2 | —<br>11·0 | —<br>11·1 |
| 11. | $p\text{-}CH_3C_6H_4$ | $p\text{-}CH_3C_6H_4$ | m.p. 80–81 | | — | — | 278·5<br>278·6 | 278·4 | −1·348 | 1·81 | 2·65 | | | | | 11·0 | |
| 12. | $CH_3$ | $C_4H_9O$ | 60·5–62 | 0·5 | 1·5298 | 1·1131 | 184·3<br>184·6 | 184·2 | −1·376 | 1·73 | 2·63 | 32·6<br>32·5 | 32·6 | 7·1<br>7·2 | 7·1 | —<br>— | — |
| 13. | $C_2H_5$ | $C_2H_5$[a] | m.p. 122·5–124 | | — | — | 179·1[b]<br>178·2 | 176·2 | −2·202 | 1·71 | 2·53 | 22·6[c]<br>22·8 | 22·6 | 6·7[c]<br>6·6 | 6·8 | —<br>— | — |
| 14. | $C_3H_7$ | $C_3H_7$ | 91–91·5 | 2 | 1·5632 | 1·0691 | 181·4<br>181·9 | 182·3 | −2·354 | 1·84 | 2·63 | 39·2<br>39·1 | 39·5 | 8·1<br>8·0 | 8·3 | 16·6<br>16·8 | 17·0 |
| 15. | $C_4H_9$ | $C_4H_9$ | 99–99·5 | 2 | 1·5481 | 1·0314 | 210·7<br>209·1 | 210·4 | −2·438 | 1·79 | 2·52 | 45·8<br>45·7 | 45·7 | 9·2<br>9·0 | 9·1 | 14·3<br>14·5 | 14·7 |
| 16. | $i\text{-}C_3H_7$[a] | $i\text{-}C_3H_7$[a] | m.p. 153–154·5 | | — | — | 206·6[b]<br>204·2 | 204·3 | −2·600 | 1·64 | 2·66 | 32·0[d]<br>31·8 | 32·4 | 7·4[e]<br>7·3 | 7·3 | —<br>— | — |

[a] Sodium salt. [b] Iodometric equivalent of the salt determined. [c] Analysis of $(C_2H_5)PSSNa\cdot 2H_2O$. [d] Analysis for Cl: Found %: 22·4, 22·3. Calc. %: 22·2. [e] Analysis of $(i\text{-}C_3H_7)_2PSSNa\cdot H_2O$. [f] $CH_3(C_3H_7\text{-}G)PSSH$ b.p. 56·5° (0·55 mm), $n_D^{20}$ 1·5400, $d_4^{20}$ 1·1430.

TABLE 5. $pK_a$ AND $K_T$ OF PHOSPHORUS THIO-ACIDS RR'PSOH ⇄ RR'POSH

| No. | R | R' | $\Sigma\sigma$ | $pKa$ | | $a = pKa - pK_1$ | | $K = 10^a - 1$ | | Thiol form in per cent | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7% Alc. | 80% Alc. | 7% Alc. | 80% Alc. | 7% Alc. | 80% Alc. | 7% | | 80% | |
| | | | | | | | | | | Present work | 7, 8 | Present work | 7, 8 |
| 1 | 2 | 3 | 4 | 5 | | 6 | | 7 | | 8 | | | |
| 1 | $C_6H_5O$ | $C_6H_5O$[a] | −0·122 | 1·50 | [b] | 0·70 | — | 4·01 | — | 80 | | 79 | |
| 2 | $CH_3O$ | $CH_3O$[c] | −0·248 | [d] | 2·80 | — | 0·47 | — | 1·95 | 74 | 72 | 68 | 22 |
| 3 | $C_2H_5O$ | $C_2H_5O$ | −0·428 | 1·49 | 2·84 | 0·41 | 0·27 | 1·57 | 0·86 | 64 | 70 | 46 | 21 |
| 4 | i-$C_3H_7O$ | i-$C_3H_7O$ | −0·582 | 1·59 | 2·90 | 0·37 | 0·13 | 1·34 | 0·35 | 54 | 74 | 29 | 25 |
| 5 | p-$ClC_6H_4$ | p-$ClC_6H_4$ | −0·584 | 1·60 | 3·00 | 0·32 | 0·22 | 1·34 | 0·66 | 54 | | 28 | |
| 6 | i-$C_4H_9O$ | i-$C_4H_9O$ | −0·600 | 1·55 | 2·94 | 0·31 | 0·14 | 1·04 | 0·38 | 52 | 76 | 27 | 26 |
| 7 | $C_3H_7O$ | $C_3H_7O$ | −0·630 | 1·55 | 2·93 | 0·28 | 0·09 | 0·91 | 0·23 | 50 | 76 | 24 | 26 |
| 8 | $C_4H_9O$ | $C_4H_9O$ | −0·822 | 1·65 | 3·14 | 0·20 | 0·05 | 0·58 | 0·12 | 38 | | 11 | |
| 9 | $CH_3$ | $C_2H_5O$ | −1·179 | 1·82 | 3·51 | | | | | 19 | 0 | 2 | 0 |
| 10 | $C_6H_5$ | $C_6H_5$ | −1·184 | 1·88 | 3·58 | | | | | 18 | | 2 | |
| 11 | $CH_3$ | i-$C_4H_9O$ | −1·265 | 1·81 | 3·69 | | | | | 16 | | 1 | |
| 12 | $CH_3$ | $C_3H_7O$ | −1·280 | 1·87 | 3·78 | | | | | 15 | | 1 | |
| 13 | $C_6H_5$ | $C_2H_5O$ | −1·315 | 1·88 | 3·72 | | | | | 14 | 0 | 1 | 0 |
| 14 | $CH_3$ | $C_4H_9O$ | −1·376 | 1·95 | 3·77 | | | | | 12 | | 0·8 | |
| 15 | $C_3H_7$ | $C_2H_5O$ | −1·391 | 2·00 | 3·81 | | | | | 12 | 0 | 0·7 | 0 |
| 16 | $C_4H_9$ | $C_2H_5O$ | −1·433 | 2·11 | 3·95 | | | | | 10 | 0 | 0·6 | 0 |
| 17 | $C_2H_5$ | $C_4H_9O$ | −1·512 | 2·21 | 4·01 | | | | | 9 | | 0·4 | |
| 18 | i-$C_4H_9$ | $C_4H_9O$ | −1·708 | 2·20 | 4·29 | | | | | 5 | | 0·2 | |
| 19 | $C_2H_5$ | $C_2H_5$ | −2·202 | 2·80 | 4·88 | | | | | 1 | | 0·1 | |
| 20 | $C_3H_7$ | $C_3H_7$ | −2·354 | 2·83 | 5·10 | | | | | 1 | | 0 | |
| 21 | $C_4H_9$ | $C_4H_9$ | −2·438 | 2·91 | 5·14 | | | | | 0·8 | | 0 | |
| 22 | i-$C_4H_9$ | i-$C_4H_9$ | −2·594 | 3·17 | 5·46 | | | | | 0·5 | | 0 | |
| 23 | i-$C_3H_7$ | i-$C_3H_7$ | −2·600 | 3·03 | 5·46 | | | | | 0·5 | | 0 | |
| 24 | s-$C_4H_9$ | s-$C_4H_9$ | −2·726 | 3·10 | 5·71 | | | | | 0·4 | | 0 | |
| 25 | t-$C_4H_9$ | t-$C_4H_9$ | −3·092 | 3·91 | 6·09 | | | | | 0 | | 0 | |

[a] The pH of triethylammonium salt solution was measured, $pK$ was calculated from the salt hydrolysis constant within ±0·1 $pK$.
[b] The $pK$ evaluation from the salt hydrolysis constant was hindered because of the unreliability of the constant $K_w$ for 80% al% alcohol.
[c] Sodium salt. [d] Data not precise due to the ready hydrolysis of the $CH_3O$ group.

Table 5 lists the deviations from linearity of acids 1 to 8 (Column 6) as well as the tautomeric equilibrium constants calculated therefrom in terms of equation X (Column 7). It will be seen that at high $\Sigma\sigma(\Sigma\sigma > -0{\cdot}8)$ the equilibrium is characterized by an increased amount of the thiol form, particularly in the 7 per cent aqueous alcoholic solution. In this solvent the two forms of diisobutyl thiophosphoric acid

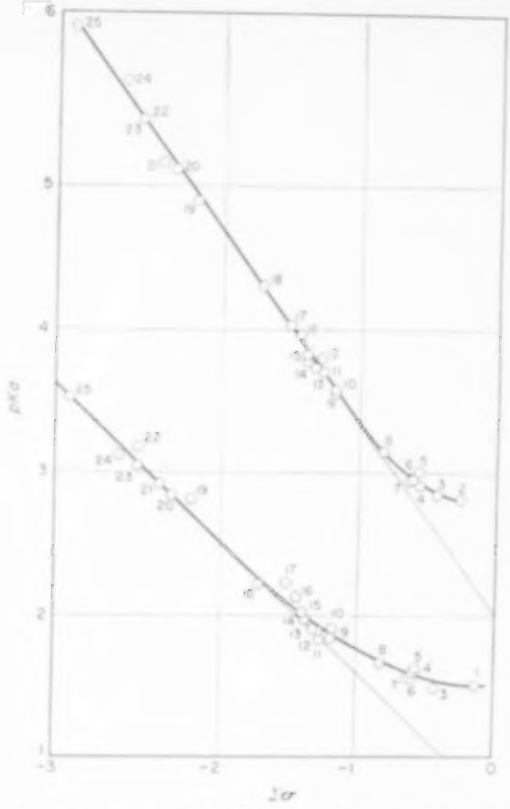


FIG. 8. A plot of $pK_a$ vs. $\Sigma\sigma$ for phosphorus monothio-acids

($\Sigma\sigma = -0{\cdot}600$) are equivalent. At still higher $\Sigma\sigma$ values the thiol form predominates, amounting to 80 per cent with diphenyl thiophosphoric acid ($\Sigma\sigma = -0{\cdot}122$). In the 80 per cent alcohol the forms are balanced at $\Sigma\sigma \simeq -0{\cdot}300$ and then the thiol form percentage is rapidly growing with increasing $\Sigma\sigma$.

The deviations from linear relationship provide thus a means to follow quantitatively the effect of the structure of phosphorus thioacids and the nature of the solvent on the equilibrium of tautomeric forms.

In turn, the tautomeric equilibrium constants must correspond to the Hammett equation

$$pK_T = pK_T^\circ - \rho_T\Sigma\sigma \qquad \text{(XI)}$$

The plot of $pK_T$ versus $\Sigma\sigma$ in 7 per cent and 80 per cent alcohol is given in Fig. 9. It will be seen that the linearity is fairly good. The conventional treatment resulted

for 7 per cent alcohol in log $K_T^\circ = 0{\cdot}74$, $\rho_T = 1{\cdot}172$, $r = 0{\cdot}970$ and for 80 per cent alcohol: log $K_T^\circ = 0{\cdot}85$, $\rho_T = 2{\cdot}139$, $r = 0{\cdot}961$.

These data allow to calculate the percentage of thiol forms of all compounds under investigation in 7 per cent and 80 per cent alcohol, the data being listed in Table 5, Column 8.

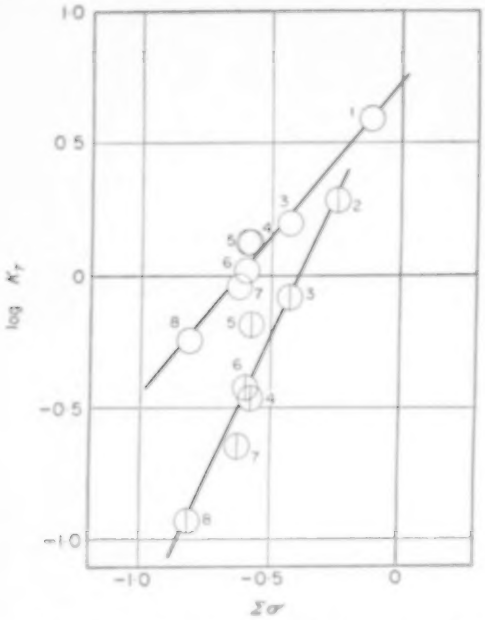


FIG. 9. A plot of p$K_T$ vs. $\Sigma\sigma$ for phosphorus thio-acids

In the same column (8) are listed comparative data previously obtained with some acids using another method.[7,8*] The agreement is seen to be rather satisfactory particularly if one bears in mind that the two methods are based on different principles.

* These data were previously obtained starting from the concept that the Brønsted equation is strictly valid for organo-phosphorus acids.[7,8] Our investigation of a great number of compounds has however shown that the slope of the straight line $pK_{s_1} = \alpha pK_{s_2} + \text{const.}$ for acids RR′POOH is not equal to 45°, but somewhat differs from it. As to acids RR′PSSH, the overlapping of the ionization constants of different acids of this type in the 7 per cent and 80 per cent alcohol makes it extremely difficult to plot the Brønsted straight line. Therefore these data cannot be claimed to be exact.

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# DER NACHWEIS DER ZWISCHENSTUFE BEI NUCLEOPHILEN AROMATISCHEN SUBSTITUTIONEN MIT ELIMINIERUNG; ZUR STRUKTUR DER ARINE*

R. HUISGEN, W. MACK[1] und L. MÖBIUS[2]
Institut für Organische Chemie der Universität München

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**Zusammenfassung**—Bei der Freisetzung des Benz-ins aus Fluor- oder Chlorbenzol ist Lithiumpiperidid in Äther bei 20° 27 bzw. 70 mal aktiver als Phenyllithium. Andererseits addiert das Benz-in, wie Konkurrenzversuche zeigen, das Phenyllithium 4·4 mal rascher als Lithiumpiperidid. Diese Diskrepanz zwischen Bruttoreaktionsgeschwindigkeit und Produktbildung beweist das Auftreten einer auswahlfähigen Zwischenstufe. Da die Natur des Halogens die Reaktivität nicht beeinflusst, muss die Zwischenstufe halogenfrei sein.

Im gleichen System, Phenyllithium/Lithiumpiperidid in Äther, zeigen 1,2-Naphthin und 9,10-Phenanthrin mit 5·8 bzw. 12·8 höhere Konkurrenzkonstanten. Die steigende Selektivität der Arine geht auf die zunehmende Bindungsenergie der Zwischenstufe als Folge der Verkürzung des CC-Abstandes zurück.

**Abstract**—Lithium piperidide in ether at 20° is 27 times more efficient in the formation of benzyne from fluorobenzene, and 70 times more efficient with chlorobenzene than is phenyllithium. On the other hand, as competition experiments reveal, benzyne adds phenyllithium 4·4 times as readily as lithium piperidide. This discrepancy between rate of benzyne formation and rate of addition establishes the presence of a selective intermediate. The nature of the halogen in the aryl halide does not influence the product composition. Therefore, the intermediate is regarded as halogen free.

In the same system, phenyllithium and lithium piperidide in ether, 1,2-naphthyne and 9,10-phenanthryne show higher competition constants of 5·8 and 12·8 respectively than benzyne. The increasing selectivity of the arynes is the result of an increasing bond energy which stems from a decreasing bond distance.

## (A) *Zum Eliminierungsmechanismus der nucleophilen aromatischen Substitution*

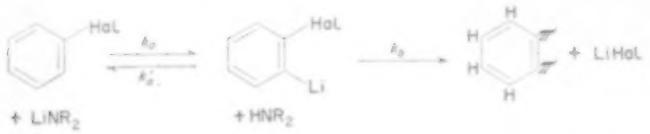
Die schon von Wittig[3] vermutete nucleophile aromatische Substitution mit primärer Eliminierung wurde in den Jahren 1953/54 von Roberts und Mitarbb.[4] für die Aminierung der Halogenbenzole sowie von Huisgen und Rist[5] für die Reaktion der Fluoraromaten mit Phenyllithium experimentell gesichert. Die charakteristischen Umlagerungen unter Einbeziehung der *o*-Positionen dienten als Indiz. In zahlreichen Arbeiten wurden seitdem die Gültigkeitsgrenzen dieses bedeutsamen neuen Substitutionsmechanismus abgesteckt und dessen präparative Nutzbarkeit studiert.[6] Der

* Nucleophile aromatische Substitutionen, XV; XIV. Mitteil.: R. Huisgen, W. Mack, K. Herbig, N. Ott und E. Anneser, *Chem. Ber.* **93**, im Druck (1960).

[1] Aus der Dissertat. W. Mack, Universität München (1959).
[2] Aus der Diplomarbeit L. Möbius, Universität München (1959).
[3] G. Wittig, *Naturwissenschaften* **30**, 696 (1942).
[4] [a] J. D. Roberts, H. E. Simmons, L. A. Carlsmith und C. W. Vaughan, *J. Amer. Chem. Soc.* **75**, 3290 (1953); [b] J. D. Roberts, D. A. Semenow, H. E. Simmons und L. A. Carlsmith, *Ibid.* **78**, 601 (1956).
[5] R. Huisgen und H. Rist, *Naturwissenschaften* **41**, 358 (1954); *Liebigs Ann.* **594**, 137 (1955); R. Huisgen und H. Zirngibl, *Chem. Ber.* **91**, 1438 (1958).
[6] Vgl. die Zusammenfassungen von G. Wittig, *Angew. Chem.* **69**, 245 (1957); J. F. Bunnett, *Quart. Rev.* **12**, 1 (1958); E. F. Jenny, M. C. Caserio und J. D. Roberts, *Experientia* **14**, 349 (1958); R. Huisgen und J. Sauer, demnächst in *Angew. Chem.*

klassische Additions- und der neue Eliminierungsmechanismus der nucleophilen aromatischen Substitution wurden gelegentlich in Konkurrenz gefunden, so bei der Umsetzung der Fluornaphthaline mit Alkaliamiden[7] oder der alkalischen Hydrolyse des Chlorbenzols.[8]

Für mechanistische Untersuchungen erwies sich die Reaktion der Halogenaromaten mit Lithium-dialkylamiden in Äther als günstiges Studienobjekt. Die Lithiumbase setzt unter HHal-Abspaltung die als *Arin* (aryne) bezeichnete Zwischenstufe frei und addiert sich anschliessend an diese. Wenn man die entstehende lithiumorganische Verbindung rasch mit freiem sekundären Amin entmetalliert, gelangt man zu den Aryl-dialkylaminen in guter Ausbeute.[9] Kinetische Studien sprechen für einen einheitlichen Chemismus der Arinbildung aus Halogenaromaten mittels lithiumorganischer Verbindungen oder Lithium-dialkylamiden.[10] Danach ist die *o*-Metallierung mit $k_a$ stets der langsamste Teilschritt; Lithiumhalogenid-Abspaltung ($k_b$) zum Arin und Entmetallierung zum Arylhalogenid ($k_a'$) konkurrieren in raschen Folgereaktionen um das *o*-Lithium-halogenbenzol: Bei Brom- und Jodbenzol ist




die LiHal-Abgabe so schnell, dass allein die einleitende Metallierung die Reaktionsgeschwindigkeit (RG) bestimmt.[10] Die Geschwindigkeitskonstanten der Arinbildung aus Arylbromiden werden daher von den *CH-Aciditäten* der aromat. Verbindungen diktiert.[11]

Welche Kriterien kennzeichnen nun das Arin als *Zwischenstufe*, also als *Delle im Energieprofil* der Substitutionsreaktion? Es gibt mehrere Möglichkeiten, Zwischenstufen nachzuweisen. Die erste beruht auf der Wahl eines geeignet substituierten Modellsystems mit so tiefem "Energietopf", dass die Zwischenstufe mit physikalischen Methoden charakterisiert oder gar in Substanz isoliert werden kann. Dieser Weg erscheint bei den Arinen hoffnungslos, solange dieselben nur über metallorganische Verbindungen zugänglich sind. Alle metallorganischen Reagentien addieren sich nämlich ausserordentlich rasch an Arine.

Eine andere Nachweismöglichkeit der Zwischenstufe gründet sich auf deren Fähigkeit, den Partner für die Weiterreaktion frei auszuwählen. Diese Fähigkeit wird im *Konkurrenzversuch* geprüft; eine Diskrepanz zwischen Reaktionsgeschwindigkeit und Produktbildung macht die Zwischenstufe evident. Solche Konkurrenzversuche ermöglichten beispielsweise den Nachweis der Carbonium-Zwischenstufe bei $S_N1$-Reaktionen.[12]

[7] R. Huisgen und J. Sauer, *Angew. Chem.* **69**, 390 (1957); R. Huisgen, J. Sauer, W. Mack und I. Ziegler, *Chem. Ber.* **92**, 441 (1959); J. F. Bunnett und T. K. Brotherton, *J. Amer. Chem. Soc.* **78**, 6265 (1956).
[8] A. T. Bottini und J. D. Roberts, *J. Amer. Chem. Soc.* **79**, 1458 (1957); vgl. A. Lüttringhaus und D. Ambros, *Chem. Ber.* **89**, 463 (1956).
[9] [a] R. Huisgen und J. Sauer, *Chem. Ber.* **91**, 1453 (1958); [b] J. Sauer, R. Huisgen und A. Hauser, *Ibid.* **91**, 1461 (1958).
[10] R. Huisgen und J. Sauer, *Chem. Ber.* **92**, 192 (1959).
[11] R. Huisgen, W. Mack, K. Herbig, N. Ott und E. Anneser, *Chem. Ber.* im Druck
[12] L. C. Bateman, E. D. Hughes und C. K. Ingold, *J. chem. Soc.* 960, 974 (1940); Vgl. C. K. Ingold, *Structure and Mechanism* S. 350–355, 360–373. Bell, London (1953).

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(B) *Konkurrenzversuche mit Benz-in*

Normalerweise addiert sich das Arin-freisetzende Agens anschliessend an die Zwischenstufe. Ausnahmen sind bekannt. Die Bildung des Diphenylamins aus Chlorbenzol, Kaliumamid und Kaliumanilid in flüss. Ammoniak[13] interpretiert man heute mit einer Freisetzung des Benz-ins durch Kaliumamid und nachfolgender Addition des Kaliumanilids.

Auch die Vereinigung des Benz-ins mit Dienen nach Wittig[14] bietet ein Beispiel für die Reaktion mit Verbindungen, die zur Freisetzung des Benz-ins nicht befähigt sind. Gerade dieser Autor betonte in jüngster Zeit, dass ein einwandfreier Nachweis der Arine und ihres Zwischenstufencharakters *noch nicht* vorliege.[15] Er diskutierte auch die mögliche Einbeziehung der Reaktanten in die zum Arin führende LiHal-Abspaltung; ein blosser Übergangszustand würde hier zur Produktbildung ausreichen.

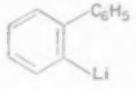
Lithiumpiperidid vermag aus Chlorbenzol in Äther bei 20° ca 70 mal rascher Benz-in freizusetzen als das stärker basische Phenyllithium.[10] Auf diese Diskrepanz zwischen RG und Basizität gründet sich ein hübsches Konkurrenzphänomen, das wir als "katalytische Phenylierung" der Chloraromaten bezeichneten.[16] Die langsame Biphenyl-Bildung aus Chlorbenzol und Phenyllithium lässt sich durch bescheidenen Piperidin-Zusatz beschleunigen. Das momentan aus Piperidin und Phenyllithium erzeugte Lithiumpiperidid setzt aus Chlorbenzol das Benz-in rasch frei. Bei der anschliessenden Konkurrenz der beiden Lithiumbasen um Benz-in ist das Phenyllithium erfolgreicher:

$$HNC_5H_{10} + LiC_6H_5 \rightarrow C_6H_6 + LiNC_5H_{10} \quad (1)$$

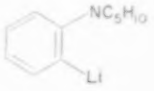
$$C_6H_5Cl + LiC_6H_5 \rightarrow C_6H_4 + LiCl + C_6H_6 \quad (2)$$

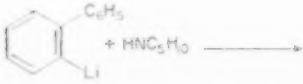
$$C_6H_5Cl + LiNC_5H_{10} \rightarrow C_6H_4 + LiCl + HNC_5H_{10} \quad (3)$$

$$C_6H_4 + LiC_6H_5 \longrightarrow \quad (4)$$




$$C_6H_4 + LiNC_5H_{10} \longrightarrow \quad (5)$$




(6)

Die Summierung von (3), (4) und (6) zeigt die katalytische Funktion des Amins bzw. Lithiumamids:

$$C_6H_5Cl + LiC_6H_5 \rightarrow C_6H_5{-}C_6H_5 + LiCl \qquad (3 + 4 + 6)$$

[13] F. W. Bergstrom, R. E. Wright, C. Chandler und W. A. Gilkey, *J. Org. Chem.* **1**, 170 (1936); R. E. Wright und F. W. Bergstrom, *Ibid.* **1**, 179 (1936).
[14] G. Wittig und L. Pohmer, *Chem. Ber.* **89**, 1334 (1956); G. Wittig und R. Ludwig, *Angew. Chem.* **68**, 40 (1956); G. Wittig und E. Knauss, *Chem. Ber.* **91**, 895 (1958).
[15] G. Wittig und H. Härle, *Liebigs Ann.* **623**, 17 (1959).
[16] R. Huisgen, J. Sauer und A. Hauser, *Angew. Chem.* **69**, 267 (1957); *Chem. Ber.* **91**, 2366 (1958).

Diese Diskrepanz zwischen Reaktionsgeschwindigkeit und Produktbildung haben wir jetzt auf eine exakte *quantitative* Basis gestellt. Die aus Quecksilber-diphenyl und Lithium bereiteten, salzfreien Phenyllithium-Lösungen ergaben nach Gehaltsbestimmung und Umsetzung mit gewogenen Piperidin-Quantitäten ca. 1 m-Ätherlösungen mit genau bekannten Verhältnissen an Phenyllithium und Lithiumpiperidid. Wir brachten Chlor- oder Fluorbenzol mit dem 10-12-fachen Überschuss an den beiden Lithiumbasen in siedendem Äther zur Reaktion. Im Anschluss an die Hydrolyse wurde destilliert und in basische und neutrale Produkte getrennt; die IR-Analyse lieferte die in Tabelle 1 angeführten Ausbeuten an Biphenyl und N-Phenylpiperidin.

TABELLE 1. KONKURRENZVERSUCHE DER HALOGENAROMATEN MIT ÜBERSCHÜSSIGEM PHENYLLITHIUM UND LITHIUMPIPERIDID IN SIEDENDEM ÄTHER. IR-ANALYSE DER PRODUKTE

| Nr. | mMol Ar-Hal | | mMol Lithiumbasen $LiC_6H_5$ | mMol Lithiumbasen $LiNC_5H_{10}$ | mMol Produkte $Ar\text{-}C_6H_5$ | mMol Produkte $Ar\text{-}NC_5H_{10}$ |
|---|---|---|---|---|---|---|
| (a) *Versuche in salzfreier Ätherlösung* | | | | | | |
| 1 | 20 | Fluorbenzol | 78·0 | 150 | 9·55 | 4·85 |
| 2 | 20 | Fluorbenzol | 75·0 | 150 | 9·18 | 5·00 |
| 3 | 10 | Fluorbenzol | 89·5 | 70·0 | 6·70 | 1·43 |
| 4 | 10 | Fluorbenzol | 56·9 | 95·5 | 4·90 | 2·06 |
| 5 | 20 | Chlorbenzol | 100 | 100 | 14·3 | 3·80 |
| 6 | 20 | Chlorbenzol | 90·0 | 120 | 11·65 | 4·18 |
| 7 | 20 | 1-Fluornaphthalin | 75·0 | 150 | 11·08 | 4·88 |
| 8 | 20 | 1-Fluornaphthalin | 60·0 | 180 | 9·30 | 6·07 |
| 9 | 10 | 1-Fluornaphthalin | 89·5 | 70·0 | 8·73 | 1·53 |
| 10 | 10 | 1-Fluornaphthalin | 56·8 | 95·5 | 7·11 | 2·29 |
| 11 | 15 | 9-Chlorphenanthren | 102·5 | 105 | 11·0 | 1·00 |
| 12 | 15 | 9-Chlorphenanthren | 130·5 | 100 | 11·0 | 0·75 |
| 13 | 10 | 9-Chlorphenanthren | 71·5 | 114 | 6·04 | 0·83 |
| (b) *Versuche in* LiBr*-haltiger Ätherlösung* | | | | | | |
| 14 | 20 | Fluorbenzol | 100 | 100 | 9·40 | 3·56 |
| 15 | 20 | Fluorbenzol | 50·0 | 150 | 4·60 | 6·70 |
| 16 | 20 | Chlorbenzol | 100 | 100 | 10·0 | 3·72 |
| 17 | 20 | Chlorbenzol | 50·0 | 150 | 3·72 | 6·70 |
| 18 | 10 | 9-Fluorphenanthren | 100 | 100 | 5·40 | 0·54 |
| 19 | 10 | 9-Fluorphenanthren | 150 | 50 | 6·73 | 0·256 |
| 20 | 9.2 | 9-Chlorphenanthren | 40 | 160 | 2·33 | 1·22 |

Bei freier Konkurrenz der Lithiumbasen um die Zwischenstufe Benz-in gilt, dem Massenwirkungsgesetz folgend:

$$\frac{d(C_6H_5 \cdot C_6H_5)}{dt} = k_2(\text{Benz-in})(LiC_6H_5) \tag{7}$$

$$\frac{d(C_6H_5 \cdot NC_5H_{10})}{dt} = k_2'(\text{Benz-in})(LiNC_5H_{10}) \tag{8}$$

$$\frac{d(C_6H_5 \cdot C_6H_5)}{d(C_6H_5 \cdot NC_5H_{10})} = \frac{k_2}{k_2'} \frac{(LiC_6H_5)}{(LiNC_5H_{10})} \tag{9}$$

Da die Konzentrationen an Phenyllithium und Lithiumpiperidid — die Lithiumbasen befinden sich in grossem Überschuss — in erster Näherung konstant sind, ist der Übergang von den Differentialen zu den Differenzen bzw. zu den Gesamtausbeuten erlaubt. Das Ausbeuteverhältnis von Biphenyl und Phenylpiperidin sollte somit eine *lineare Funktion* des Verhältnisses der Lithiumbasen sein, wobei die Steigung der Geraden dem Quotienten der spezifischen Additionsgeschwindigkeiten entspricht.

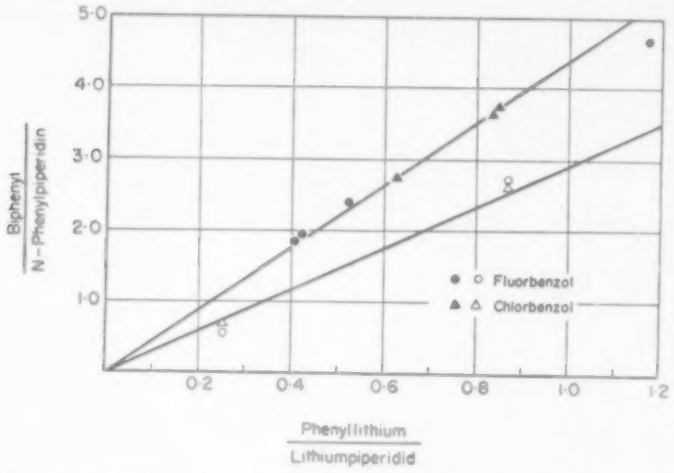



FIG. 1. Konkurrenz von Phenyllithium und Lithiumpiperidid in der Addition an Benz-in. Die Konzentrationen der Lithiumbasen sind gemäss (10) korrigiert. ● und ▲ beziehen sich auf Versuche in LiBr-freier Lösung; bei den Versuchen ○ und △ war (LiBr) = ($LiC_6H_5$) + ($LiNC_5H_{10}$).

Zu einer besseren Näherung (10) gelangt man, wenn man statt der Anfangskonzentrationen der Lithiumbasen diejenigen nach 50% Umsatz verwendet und berücksichtigt, dass letztlich die ganze Arin-Freisetzung auf Kosten des Phenyllithiums erfolgt.

$$\frac{(C_6H_5{\cdot}C_6H_5)}{(C_6H_5{\cdot}NC_5H_{10})} = \frac{k_2}{k_2'}\,\frac{(2LiC_6H_5 - C_6H_5Hal - C_6H_5{\cdot}C_6H_5)}{(2LiNC_5H_{10} - C_6H_5{\cdot}NC_5H_{10})} \qquad (10)$$

Nach Fig. 1 bestimmen die Messpunkte für Chlorbenzol und Fluorbenzol tatsächlich *eine durch den Koordinatenschnittpunkt führende Gerade*. Die mit der Steigung gleichzusetzende Konkurrenzkonstante beträgt 4·4, d.h. das Benz-in gibt dem Phenyllithium bei der Addition einen 4·4-fachen Vorzug vor dem Lithiumpiperidid. Stellt man dieses Phänomen den Bruttoreaktionsgeschwindigkeiten gegenüber—Phenyllithium setzt das Benz-in 27 bzw. 70 mal langsamer aus Fluor- bzw. Chlorbenzol frei als Lithiumpiperidid[10],—dann liegt in dieser Diskrepanz das untrügliche Kennzeichen der *auswahlfähigen Zwischenstufe*.

Kann das *o*-Lithium-halogenbenzol die auswahlfähige Zwischenstufe sein? Schon oben wurde betont, dass die Brutto-RG im wesentlichen von der Bildung dieser *o*-metallierten Verbindung bestimmt wird. Triftige Gründe sprechen dagegen, dieser Zwischenstufe die für die Produktbildung verantwortliche Auswahlfähigkeit zuzuschreiben. Die Konkurrenzkonstante ist gemäss Abbild. 1 für Fluor- und Chlorbenzol gleich. Auch wenn die Addition der Lithiumbase an ein Arin von geringerer

Bindungssymmetrie zu 2 stellungsisomeren Produkten führt, lässt die Halogenvariation im eingesetzten Arylhalogenid *keinen* Einfluss auf das Isomerenverhältnis erkennen. So liefern etwa *p*-Fluor-, *p*-Chlor- und *p*-Brom-toluol mit Lithiumpiperidid bei starken Unterschieden in der Reaktionsgeschwindigkeit ein und dasselbe Gemisch von N-[*m*-Tolyl]- und N-[*p*-Tolyl]-piperidin.[9a] Das aus 1- oder 2-Chlor-, -Brom- oder Jodnaphthalinen hervorgehende Gemisch von 1- und 2-Piperidino-naphthalin ist mit 31 : 69% unabhängig von Stellung und Natur des Halogens.[9b] Auch die Umsetzung von Halogenbenzol-[1-$^{14}$C] mit Kaliumamid in flüss. Ammoniak lieferte die Isotopisomeren in einem vom Halogen (Cl, J) unabhängigen Verhältnis.[4b]

Wir schliessen daraus, dass die auswahlfähige Zwischenstufe *das Halogen nicht mehr enthält*. Da eine metallverbrückte kationische Zwischenstufe wenig wahrscheinlich ist,[17] gibt sich die oben nachgewiesene, auswahlfähige Zwischenstufe als das Produkt der HHal-Eliminierung aus Halogenbenzol, das Benz-in $C_6H_4$, zu erkennen.

Bei unseren ersten Konkurrenzversuchen im System Phenyllithium/Lithiumpiperidid enthielt die ätherische Lösung eine den Lithiumbasen äquivalente Menge *Lithiumbromid*, von der Darstellung des Phenyllithiums aus Brombenzol und Lithium herrührend. Auffallenderweise bestimmen die mit Fluor- und Chlorbenzol erhaltenen Resultate (Tabelle 1, *b*) eine Gerade mit anderer Steigung, die einer Konkurrenzkonstante von 2·9 entspricht (Fig. 1). Wir vermochten jüngst zu zeigen, dass sich Lithiumpiperidid und Phenyllithium mit Lithiumhalogeniden zu ätherlöslichen, recht stabilen 1 : 1-Komplexen vereinigen, die nicht mehr zur HHal-Abspaltung aus Halogenbenzolen befähigt sind.[18] Fig. 1 bietet nun den Nachweis, dass diese Komplexbildung mit LiBr auch die Addition der Lithiumbasen an das Arin massgebend beeinflusst. Unter der unbewiesenen Annahme, dass sich nur die freien Lithiumbasen an Benz-in anlagern, lässt sich aus der verminderten Konkurrenzkonstante schliessen, dass die komplexe Bindung des Phenyllithiums durch das Lithiumbromid noch etwas stärker ist als die des Lithiumpiperidids.

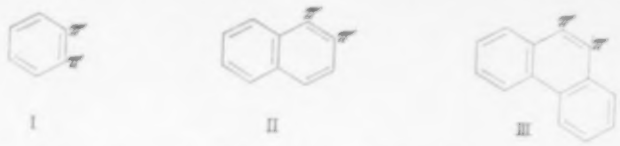
Organolithiumverbindungen[19] und Lithium-dialkylamide[20] bilden nicht nur Autokomplexe, sondern auch gemischte Komplexe.[19] Ob und wie weit diese Komplexbildung die Lithiumbasen in ihrer Fähigkeit zur Addition an das Arin beeinträchtigt, ist eine offene Frage. Möglicherweise sind die gemessenen Grössen nur *scheinbare* Konkurrenzkonstanten. Der unten beschriebenen Auswertung solcher Konstanten tut das allerdings keinen Abbruch.

(C) *Unterschiedliche Selektivitäten der Arine*

Trotz des nicht unerheblichen experimentellen Aufwandes schien es uns lohnend, die Konkurrenzkonstanten verschiedener Arine zu vergleichen. Bieten doch diese Konstanten ein Mass für die *Selektivität* einer Zwischenstufe. Eine sehr "heisse" Zwischenstufe — die Aktivierungsenergien der Weiterreaktionen sind gering — wird nur geringe Auswahlfähigkeit entfalten und im Grenzfall statistisch mit dem nächstbesten Partner reagieren. Mit zunehmender Aktivierungsenergie steigt die Selektivität eines Reagens stark an.

Wir haben das gleiche Paar von Lithiumbasen auch in der Addition an 1·2-Naphthin (II), welches aus 1-Fluornaphthalin erzeugt wurde, konkurrieren lassen.

[17] Vgl. die Diskussion *loc. cit.*,[9a] S. 1458.
[18] R. Huisgen und W. Mack, *Chem. Ber.* **93**, im Druck (1960).
[19] F. Hein und H. Schramm, *Z. Physik. Chem.* Abt. A **151**, 234 (1930); G. Wittig, F. J. Meyer und G. Lange, *Liebigs Ann.* **571**, 184 (1951).
[20] R. Huisgen, H. König und N. Bleeker, *Chem. Ber.* **92**, 424 (1959).



I II III

Phenyllithium und Lithiumpiperidid lagerten sich in den früher beschriebenen Isomerenverhältnissen zu 1- und 2-Phenyl- bzw. 1- und 2-Piperidino-naphthalin an. Die Molverhältnisse der Lithiumbasen und die Ausbeuten an Phenyl- und Piperidino-naphthalinen gemäss IR-Analyse sind der Tabelle 1 zu entnehmen. Die Versuche Nr 7–10 definieren in Fig. 2 wiederum eine Gerade, aus deren Steigung sich eine Konkurrenzkonstante von 5·8 errechnet.

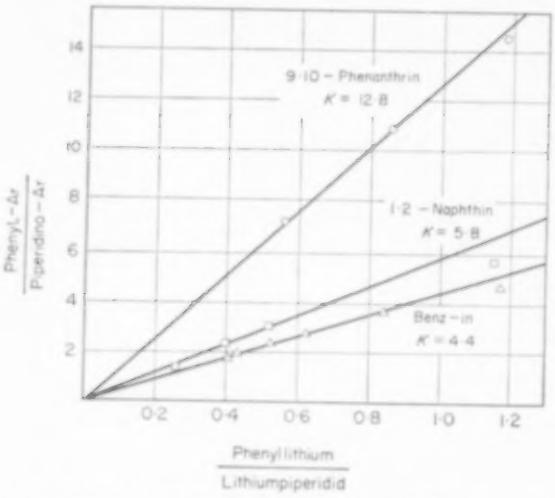



FIG. 2. Konkurrenzversuche des Phenyllithiums und Lithiumpiperidids um Benz-in (I), 1,2-Naphthin (II) und 9,10-Phenanthrin (III) in siedendem Äther. Die Konzentrationen der Lithiumbasen wurden analog (10) korrigiert.

Auf gleiche Weise liessen wir Phenyllithium und Lithiumpiperidid um 9,10-Phenanthrin (III) konkurrieren, das aus 9-Chlorphenanthren freigesetzt wurde. Die viel steilere Gerade, die sich aus den Versuchen 11–13 der Tabelle 1 ergibt, lehrt, dass III bei der Addition das Phenyllithium um den Faktor 12·8 vor dem Lithiumpiperidid bevorzugt. Versuche in LiBr-haltiger Lösung (Nr 18–20 der Tabelle 1) wiesen auf 10 als etwas niedrigere Konkurrenzkonstante.[21]

Die Konkurrenzkonstanten einiger Carbonium-ionen im System $Cl^{\ominus}/H_2O$ seien zum Vergleich angeführt:

| | |
|---|---|
| Triphenylmethyl-[22] | 3100 |
| tert. Butyl-[23] | 180 |
| Phenyl-[24] | 3 |

[21] Vorläuf. Mitteil.: Vortrag *Kekulé-Symposium*. London (1958); *Theoretical Organic Chemistry* S. 158. Butterworths, London (1958).
[22] C. G. Swain, C. B. Scott und K. H. Lohmann, *J. Amer. Chem. Soc.* **75**, 136 (1953).
[23] A. G. Ogston, E. R. Holiday, J. S. L. Philpot und L. A. Stocken, *Trans. Faraday Soc.* **44**, 45 (1948).
[24] E. S. Lewis, *J. Amer. Chem. Soc.* **80**, 1371 (1958).

Wenngleich das Phenyl-kation ein viel stärkeres Arylierungsmittel ist als Benz-in,[25] wird man auch das letztere noch aufgrund seiner niedrigen Konkurrenzkonstante als "heisses" Agens ansprechen. In der Folge Benz-in, 1,2-Naphthin und 9,10-Phenanthrin entfalten die Zwischenstufen *steigende Auswahlfähigkeit*, einer zunehmenden Tiefe des "Energietopfes" entsprechend. Welcher stabilisierende Faktor ist nun für die wachsende Selektivität der Arine in der angegebenen Folge verantwortlich?

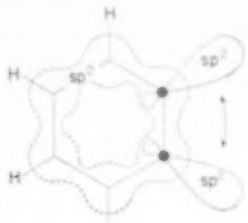



FIG. 3.

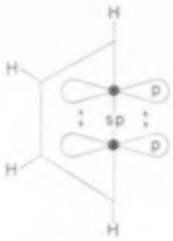



FIG. 4.

(D) *Die Struktur der Arine*

Die einleitende Eliminierung des neuen Substitutionstyps ist, soweit bisher bekannt, auf *Nachbarpositionen* des aromatischen Kerns beschränkt. Alle unsere Bemühungen andere als 1,2-Eliminierungen zu erzielen, waren erfolglos. Wir schliessen daraus, dass die beiden Extraelektronen des Arins eine, wenn auch schwache Bindung bilden. *Ohne die Energie dieser neuen Bindung scheint die Zwischenstufe des Arins nicht erreichbar zu sein.*

Der Bindungszustand des Benz-ins dürfte sich zwischen den extremen Formulierungen der Figs. 3 und 4 befinden. In einem Fall besetzen die Extraelektronen $sp^2$-Orbitals, deren bindende Wechselwirkung nur sehr schwach ist. Im anderen Extrem (Fig. 4) ermöglicht eine Verzerrung des Benzolkerns den in die Eliminierung einbezogenen Kohlenstoffatomen $\sigma$-Bindungen des sp-Typs. Die Extraelektronen entfalten hier eine mehr oder minder normale $\pi$-Bindung, allerdings um den Preis einer extremen Ringspannung und einer gestörten Wechselwirkung der aromatischen $\pi$-Elektronen.

Auch wenn sich im Benz-in eine von den Regeln der Bindungshybridisierung erlaubte Zwischenmöglichkeit realisiert findet, entsprechen die Symmetrieeigenschaften der Extraorbitals nicht einer echten $\pi$-Bindung; sie kommen der sog. $\pi$-Bindung gespannter Cyclo-olefine nahe. Wenngleich somit unser Symbol des Arins mit den beiden $\pi$ (Formeln I–III,) auch nicht ganz korrekt ist, scheint es uns den aromatischen Charakter der Zwischenstufe stärker zu betonen und weniger zu Missverständnissen zu verleiten als die Cyclohexadienin-Formel.[3,4]

Wenn die Extrabindung des Benz-ins durch eine relativ schwache Überlappung der Orbitals zustandekommt, dann sollte sie von einer *Abstandsverkürzung* der betreffenden C-Atome erheblich profitieren. Die CC-Bindung des Benzols, die 1,2-Bindung des Naphthalins und die Phenanthren-9,10-Bindung zeigen nun eine mit steigender Bindungsordnung (*bond order*) abnehmende Bindungslänge; die Röntgenstrukturanalyse vermochte diese Abstandsverkürzung experimentell zu sichern

[25] Benz-in reagiert nur sehr zögernd mit Alkali-phenolat, während zerfallendes Benzoldiazoniumsalz schon freies Phenol leicht aryliert: R. Hirsch, *Ber. Dtsch. Chem. Ges.* **23**, 3705 (1890); DRP 58 001 (Friedländer **3**, 51 (1896)). Das Phenylkation aus Diazoniumsalz lagert sogar kovalentes Halogen an der Elektronenlücke an: A. N. Nesmeyanov, I. G. Makarova und T. P. Tolstaya, *Tetrahedron* **1**, 145 (1957).

(Tabell2). Die vom Benz-in über 1,2-Naphthin zum 9,10-Phenanthrin zunehmende Stabilisierung, die sich in steigender Selektivität äussert, geht somit auf die wirksamere Überlappung der Extraorbitals als Folge der Bindungsverkürzung zurück.

## EXPERIMENTELLER TEIL

### LiBr-*freies Phenyllithium*

Die Vorschrift von Schlenk und Holtz[28] ist für die Herstellung grösserer Quantitäten wenig geeignet und wurde folgendermassen modifiziert:

10 g Lithium werden in 50 cc Paraffinöl im 200 cc-Weithalskolben bei 210° (Innentemp.) unter Stickstoffdusche mit dem Ultraturrax (Fa. Janke u. Kunkel) bei mässiger Drehzahl zerstäubt, wobei

Tabelle 2. Beziehung der Arin-Selektivitäten zu den Bindungsordnungen in den zugehörigen Kohlenwasserstoffen

| | Benzol | Naphthalin-1,2 | Phenanthren-9,10 |
|---|---|---|---|
| Bindungsordnung[26] | 1·667 | 1·725 | 1·80 |
| Bindungslänge in Å | | | |
| Ber.[27] | 1·39 | 1·364 | 1·352 |
| Gef. | 1·39 | 1·365 | |
| Konkurrenzkonstante der Arine im System $LiC_6H_5/LiNC_5H_{10}$ | 4·4 | 5·8 | 12·8 |

man die Temp. langsam auf 180° fallen lässt. Nach Erkalten unter Reinstickstoff setzt man einen mit Gaseinleitungsrohr, Tropftrichter und bis zum Boden des Gefässes reichendem Heberrohr versehenen Gummistopfen auf den Kolben. Durch Eindrücken von Stickstoff trennt man die mattglänzende, obenschwimmende Metallsuspension vom Paraffinöl; auf die gleiche Weise spült man mehrfach mit Äther nach.

Rohes Quecksilberdiphenyl wurde zunächst bei 127°/0·001 Torr destilliert, dann aus dem 10-fachen Gewicht Äthanol umkristallisiert und nochmals destilliert.

In einem 1 l-Dreihalskolben mit Intensiv-Rückflusskühler und Rührer legt man die oben bereitete Lithiumsuspension in 600 cc abs. Äther vor. Nach Zugabe von 10 g gepulv. Quecksilberdiphenyl rührt man 1–2 Min unter Reinstickstoff bis zum Anspringen der Reaktion, kenntlich an der Schwarzfärbung und dem spontanen Aufsieden des Äthers. Bei guter Eiskühlung trägt man nun portionsweise innerhalb 15–20 Min weitere 130 g Quecksilberdiphenyl unter Stickstoffdusche und Rühren ein. Anschliessend rührt man 30 Min unter Eiskühlung und erwärmt noch 5 Min zum gelinden Rückflusssieden. Nach Erkalten füllt man vorsichtig in eine Phenyllithium-Bürette ab; die nach Absitzen des Niederschlags klare, hellgelbe Lösung wird im Kühlschrank aufbewahrt.

Der im Kolben verbliebene schwarze Schlamm, der an der Luft selbstentzündlich ist, wird mit 100 cc Petroläther und tropfenweise mit Methanol bis zum Abschluss der Wasserstoffentwicklung versetzt; die Ammoniakfreisetzung rührt von der nicht störenden Lithiumnitrid-Bildung her. Nach Zugabe von 2 N HCl trennt man 72–73 g Quecksilber im Scheidetrichter ab.

*Gehaltsbestimmung.* Die acidimetrische Titration nach Hydrolyse des Phenyllithiums erfasst auch den Anteil der Ätherspaltung. Bei Alkyllithium-Lösungen lässt sich dieser Anteil nach Zugabe von Benzylchlorid titrieren;[29] bei Phenyllithium versagt diese Methode. Nach Überführung in Lithiumpiperidid fanden wir die Halogenabspaltung aus reaktiven Arylbromiden brauchbar; Lithiumäthylat reagiert dabei nicht.

[26] C. A. Coulson, *Proc. Roy. Soc.* A **169**, 413 (1938); C. A. Coulson und H. C. Longuet-Higgins, *Rev. Sci.* **85**, 929 (1947).
[27] H. O. Pritchard und F. H. Sumner, *Proc. Roy. Soc.* A **226**, 128 (1954).
[28] W. Schlenk und J. Holtz, *Ber. Dtsch. Chem. Ges.* **50**, 262 (1917).
[29] H. Gilman und A. H. Haubein, *J. Amer. Chem. Soc.* **66**, 1515 (1944).

In einem Reaktionskölbchen, wie sie für kinetische Messungen verwendet wurden,[18] vereinigten wir 9 mMol wasserfreies Piperidin in 20 cc Äther, 3·00 cc einer ca. 1 m Phenyllithium-Lösung und 6 mMol m-*Bromanisol* unter Stickstoff. Nach 15 Min wurde hydrolysiert und das Bromidion mit 0·1 N Silbernitrat potentiometrisch titriert.[18]

Auch 9-*Bromanthracen* und m-*Bromchlorbenzol* eigneten sich als aktive Halogenverbindungen, während 9-Bromphenanthren um 2% niedrigere Werte ergab. Durchweg lieferte diese Bromidtitration 90 ± 1% des acidimetrisch ermittelten Phenyllithium-Gehalts. Die Umsetzung des Phenyllithiums mit 1,2-*Dibromäthan*[20] und Hydrolyse nach 5 Min ergab das gleiche Resultat. Auch das LiBr-haltige, aus Brombenzol bereitete Phenyllithium zeigte die Diskrepanz zwischen den beiden Methoden der Gehaltsbestimmung.

Während LiBr-haltiges Phenyllithium in Äther praktisch titerstabil ist, war bei dem LiBr-freien nach 6 Stdn Rückflusskochen in Äther mittels der Bromidmethode eine Abnahme von 3% zu verzeichnen.

Den Konkurrenzversuchen legten wir den acidimetrischen Phenyllithium-Gehalt zugrunde. Bei Umrechnung auf den Gehalt laut Bromidmethode führen die Geraden der Abbild. 1 und 2 nicht mehr durch den Nullpunkt.

### *Konkurrenzversuche mit Phenyllithium/Lithiumpiperidid Benz-in* (I)

*Versuch Nr.* 1: Im 1 l-Dreihalskolben mit Rührer und Intensivkühler wurden 209·5 cc ätherische Phenyllithium-Lösung (228 mMol) mit 15·0 cc reinem über Lithiumhydrid destillierten Piperidin (150 mMol) in 150 cc Äther unter Reinstickstoff versetzt. In die gerührte und rückflussiedende Lösung wurden 1·92 g Fluorbenzol (20·0 mMol) in 20 cc Äther eingetragen. Nach 3 Stdn Kochen und Aufbewahren über Nacht bei Raumtemp. wurde unter Eiskühlung hydrolysiert. Die mit KOH getrocknete Ätherlösung wurde über eine Drahtwendel-Kolonne bei hohem Rücklaufverhältnis bis auf ein Volumen von 25 cc abdestilliert. In einem kleinen Schwertkolben wurde der restliche Äther bei Raumtemp. abgezogen, dann das Reaktionsprodukt unter 12 Torr quantitativ übergetrieben.

Das Destillat wurde in 15 cc spektralreinem Cyclohexan gelöst und mit 3 mal 5 cc 4 N Salzsäure ausgeschüttelt; der salzsaure Auszug wurde nochmals mit 4 cc Cyclohexan ausgezogen. Die Cyclohexanlösungen wurden im Messkolben auf 25·0 cc aufgefüllt und über KOH getrocknet. Die IR-Analyse des Biphenyls erfolgte in der 0·2 mm-Fixküvette des Perkin-Elmer-Spektrophotometers (Mod. 21); im Vergleichsstrahl wurde mit Cyclohexan in gleicher Schichtdicke kompensiert. Die wie früher definierten Extinktionen[21] der Banden bei 700 und 738/cm gaben lineare Eichkurven. Von den gefundenen 1·775 g Biphenyl war der Gehalt der Phenyllithium-Lösung abzuziehen. In 100 cc Lösung der gleichen Charge wurden nach Hydrolyse und Aufarbeitung wie oben 0·1432 g Biphenyl nachgewiesen. Die korrigierte Biphenyl-Ausbeute betrug 1·475 ± 0·025 g (9·55 mMol).

Der salzsaure Auszug wurde unter Eiskühlung mit festem KOH alkalisch gemacht. Das Phenylpiperidin schüttelten wir in Cyclohexan ein, brachten die Auszüge auf 25·0 cc und unterwarfen nach Trocknen über KOH der IR-Analyse. Wiederum liessen sich die linearen Eichkurven der Banden des N-Phenylpiperidins bei 1600, 1502, 1385 und 1235/cm bequem auswerten; Vergleichspräparat N-Phenyl-piperidin.[24] Piperidin stört die Bestimmung nicht. Die Lösung enthielt 0·782 ± 0·012 g N-Phenylpiperidin (4·85 m Mol).

*Testversuche* zeigten die Zuverlässigkeit der Aufarbeitung. 2 Probetrennungen von jeweils 0·7–1·0 g Biphenyl und N-Phenylpiperidin gaben 92 und 93% des Kohlenwasserstoffs und 93·5 bzw. 95% der Base zurück. Das ausschlaggebende *Verhältnis* erfuhr demnach kaum eine Änderung.

### 1,2-*Naphthin*

*Versuch Nr.* 7 (*Tabelle* 1): Durch Zugabe von 150 mMol Piperidin zur ätherischen Lösung von 225 mMol Phenyllithium wurde eine Lösung erhalten, die Phenyllithium und Lithiumpiperidid im Verhältnis 1 : 2 enthielt. Diese Lösung in 355 cc Äther wurde mit 2·92 g 1-Fluornaphthalin (20·0 m Mol) 10 Stdn rückflussgekocht. Unter diesen Bedingungen, hohe Lithiumpiperidid-Konzentration und Abwesenheit von Piperidin, erfolgt die Substitution ganz nach dem Eliminierungsschema.[7] Nach der Hydrolyse wurde der Äther über eine Kolonne abdestilliert, anschliessend das Piperidin bis 90°/12 Torr entfernt. Die Destillation des Rückstandes lieferte bei 120–220° (Badtemp.)/10 Torr 4·55 g. 2·551 g davon wurden in IR-reinem Cyclohexan gelöst und wie oben in neutrale und basische Anteile

[20] G. Wittig und G. Harborth, *Ber. Dtsch. Chem. Ges.* **77**, 306 (1944).
[21] *loc. cit.*,[18] S. 1470; vgl. R. Huisgen und R. Grashey, *Liebigs Ann.* **607**, 46 (1957).

zerlegt. Die quant. IR-Analyse der isomeren Phenyl-naphthaline und Piperidino-naphthaline wurde schon früher[21] beschrieben. Die für 1- und 2-Piperidino-naphthalin angegebenen Banden bei 773 bzw. 744/cm erwiesen sich hier als gestört. Für den Gehalt an 2-Isomeren ergaben die Banden bei 1217, 1137 und 836/cm übereinstimmende Werte. Das 1-Piperidino-naphthalin liess sich nicht genau bestimmen und wurde auf der Grundlage des früher ermittelten Isomerenverhältnisses (30 : 70[6]) berechnet. Analysenresultate (auf die Gesamtausb. bezogen): 0·823 g 1-Phenyl (4·03 mMol) und 1·44 g 2-Phenylnaphthalin (7·05 mMol); 0·720 g 2-Piperidino-naphthalin 3·42 mMol); für das 1-Isomere ber. 0·309 (1·46 mMol).

### 9,10-*Phenanthrin*

Vergleichspräparate: 9-*Phenyl-phenanthren*.[16] 9-[*N-Piperidino*]-*phenanthren*: Vorteilhafter als die thermische Umsetzung des 9-Bromphenanthrens mit Piperidin[22] ist die Reaktion mit Lithiumpiperidid.[23] In die sied. Lösung von 8·50 g 9-Chlorphenanthren (40 mMol) und 15·8 cc wasserfreiem Piperidin in 100 cc Äther wurden 90 mMol Phenyllithium in Ätherlösung (88 cc) innerhalb 3 Stdn eingetropft. Nach weiteren 3 Stdn Rückflusskochen hydrolysierten wir die rote Lösung und trennten Neutral- und Basenanteil. Neben 0·21 g Phenanthren (3% d.Th.) fielen 9·02 g 9-Piperidino-phenanthren (87% d.Th.) mit Sdp. 162–164°/0·001 Torr an; aus Äthanol farbl. Stäbchen mit Schmp. 116–116·5° (Lit[22] 113°). Das aus Alkohol in gelben Nadeln kristallisierende Pikrat zeigt Zersp. 185°.

*Versuch Nr.* 13 (Tabelle 1): 2·13 g 9-Chlorphenanthren (10·0 mMol) wurden wie oben mit 71·5 mMol Phenyllithium und 114 mMol Lithiumpiperidid in 370 cc Äther 1 Stde bei Siedetemp. und 15 Stdn bei Raumtemp. umgesetzt. Nach Hydrolyse und Entfernen des Äthers wurden das Piperidin und das mit dem Phenyllithium eingeschleppte Biphenyl bis 180° (Badtemp.)/12 Torr abdestilliert. Die Hochvakuumdestillation gab bei 130–230°/0·001 Torr 2·48 g kristallin erstarrendes Produkt. Der Lösung in 30 cc spektralreinem Cyclohexan wurde das tertiäre Amin mit 5 mal 8 cc halbkonz. Salzäure entzogen. In der auf 50 cc aufgefüllten Cyclohexanlösung des Neutralprodukts analysierten wir das 9-Phenyl-phenanthren mittels der IR-Bande bei 700 und 745/cm: 1·54 ± 0·02 g (6·04 mMol). Für die IR-Analyse des 9-Piperidino-phenanthrens in 25 cc Cyclohexan waren die Banden 728 und 768/cm geeignet, wobei mit künstlichen Mischungen eingegrenzt wurde: 0·216 g ± 0·005 (0·83 mMol). Gl. (10) führte zur Konkurrenzkonstante 13·0.

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[22] E. Lellmann und M. Büttner, *Ber. Dtsch. Chem. Ges.* **23**, 1383 (1890).
[23] Aus der Dissertat. A. Hauser, Universität München (1959)

Tetrahedron, 1960, Vol. 9, pp. 40 to 52. Pergamon Press Ltd. Printed in Northern Ireland

# CONFORMATIONAL ANALYSIS OF ALICYCLIC COMPOUNDS—I

## CONSIDERATIONS OF MOLECULAR GEOMETRY AND ENERGY IN MEDIUM AND LARGE RINGS

R. PAUNCZ and D. GINSBURG
Department of Chemistry, Israel Institute of Technology, Haifa, Israel

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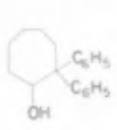
**Abstract**—The geometry of certain conformations of medium ring cyclo-alkanes and cyclo-alkenes is evaluated by vector methods. Using a potential function for the non-bonded H . . H interactions, the energies of the relevant conformations are compared. The effect of deformations is discussed.

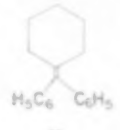
IN the recent decade much progress has been made in understanding the stereochemistry of alicyclic systems containing six-membered rings, the impetus having been afforded in many cases by studies of natural products.[1]

The application of this rapidly growing body of knowledge to larger rings has been sporadic. Even the investigators who have contributed most to the field of medium-ring compounds have been wary in extending, by analogy, considerations obtaining in the cyclohexane ring to, e.g. cyclo-octane, cyclononane or cyclodecane compounds.[2] Whilst certain fixed conformations may be used to explain various reactions of the systems involved, it is clear from recent work that the conformational problems in larger rings are more complex than immediately apparent, although superficially it often appears that direct analogies may be made.

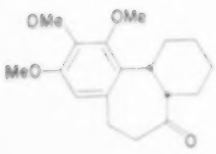
For example, the dehydration, accompanied by ring contraction of 2,2-diphenylcycloheptanol (I) to afford benzhydrylidenecyclohexane (II),[3] can be explained



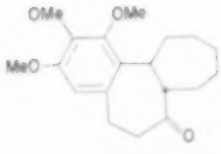

I



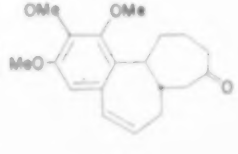

II




III




IV




V

[1] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953); W. Klyne, *Progress in Stereochemistry* Vol. 1 pp. 36–89. Butterworths, London (1954); W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) pp. 1–60. John Wiley, New York (1956).

[2] V. Prelog, in Todd, *Perspectives in Organic Chemistry* pp. 96–133. Interscience, New York (1956); V. Prelog, *Paris Congress lecture, in Experientia Supplementum* VII pp. 261–274. Birkhauser Verlag, Basel (1957)

[3] R. E. Lyle and R. A. Covey, *J. Amer. Chem. Soc.* 75, 4973 (1953); C. D. Gutsche, N. N. Saha and H. F Johnson, *Ibid.* 79, 4441 (1957).

completely in analogy to the argument used for the dehydration of 3$\beta$-hydroxytriterpenes which give the isopropylidenecyclopentane a ring in the corresponding products. Yet, there are differences in behaviour as compared to cyclohexanes, stemming from additional considerations unique to the cycloheptane ring. For example,[4] the highly stereospecific metal hydride reductions of the cycloheptanones III, IV and V in all cases giving the "axial" alcohol, as well as other stereospecific reactions in similar compounds can best be explained by assuming that the cycloheptane and cycloheptene rings in these compounds possess a rigid chair conformation.

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As one step in our own studies on conformations of medium and large rings, we present a simple method of calculating the geometry of various conformations and using this method we discuss some of the plausible conformations.

*Geometry of the molecules*

The most striking stereochemical relations for a given conformation may easily be visualized by employing simple mechanical models.[5] However, in many cases more accurate interatomic distances are needed. This requires evaluation of the molecular geometry. Corey and Sneen[6] have proposed a method for treating this problem using simple trigonometric and vector relations. This method is reconsidered only for certain conformations of cyclo-alkanes and cyclo-alkenes which possess some symmetry since it is simpler at the outset to consider symmetrical models.

*The method of calculation*

*Cyclo-alkanes.* In the first step we assume:

(i) a constant C–C bond length, $c = 1{\cdot}542$ A°
(ii) a constant C–H bond length, $d = 1{\cdot}093$ A°
(iii) tetrahedral valency angles, $\gamma = 109° 28'$

Subsequently we consider the possibility and effect of small deformations.

*Notation.* We number the carbon atoms of the molecule from 1 to $n$ and denote the vector connecting the $i$th C atom with the $(i + 1)$-st by $\mathbf{C}_{i,i+1}$. All these vectors have the same magnitude ($c$) and their vector sum is zero, as we are dealing with a closed polygon

$$\sum_{i=1}^{n} \mathbf{C}_{i,i+1} = 0 \tag{1}$$

the co-ordinates of the $(n + 1)$-st C atom being indentical with those of the first.

Denote the vectors pointing from the $i$th C atom towards the corresponding H atoms by $\mathbf{r}_i$ and $\mathbf{s}_i$, using the convention that $\mathbf{r}_i$ is above and $\mathbf{s}_i$ is below the plane determined by $\mathbf{C}_{i-1,i}$ and $\mathbf{C}_{i,i+1}$. Their magnitude is $d$.

On the basis of assumptions *i–iii* we have the following relations:

$$(\mathbf{C}_{i,i-1}\mathbf{C}_{i,i+1}) = c^2 \cos\gamma \tag{2}$$

$$(\mathbf{r}_i\mathbf{s}_i) = d^2 \cos\gamma \tag{3}$$

$$(\mathbf{C}_{i,i+1}\mathbf{r}_i) = (\mathbf{C}_{i,i+1}\mathbf{s}_i) = (\mathbf{C}_{i,i-1}\mathbf{r}_i) = (\mathbf{C}_{i,i-1}\mathbf{s}_i) = cd \cos\gamma \tag{4}$$

where $(\ldots\ldots)$ denotes the scalar product of the vectors.

[4] H. J. E. Loewenthal, private communication.
[5] Ingeniously constructed models due to A. Dreiding are now available commercially from W. Büchi, Flawil, Switzerland.
[6] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* 77, 2505 (1955).

Evaluation of the molecular geometry may be divided into two steps:
(1) Determination of the C–C skeleton, i.e. the vectors $\mathbf{C}_{i,i+1}; i = 1 \ldots n$ which satisfy relations (1) and (2).
(2) Calculation of the vectors $\mathbf{r}_i$ and $\mathbf{s}_i$, satisfying relations (3) and (4). The latter determine the positions and the distances between the hydrogen atoms. Assuming that the actual conformation is governed by the H . . . H non-bonded interactions and using a semi-empirical potential function for these interactions, we can use the molecular geometry to evaluate the energy of the non-bonded interaction. This affords information with regard to the stability of various conformations.

First we show that step (2) may be simply solved if step (1) is given. We introduce two subsidiary unit vectors $\mathbf{h}_i$ and $\mathbf{n}_i$, defined as follows:

$$\mathbf{h}_i = \frac{1}{2c \cos \gamma/2} (\mathbf{C}_{i-1,i} - \mathbf{C}_{i,i+1}) \tag{5}$$

$$\mathbf{n}_i = \frac{1}{c^2 \sin \gamma} [\mathbf{C}_{i-1,i} \mathbf{C}_{i,i+1}] \tag{6}$$

$[\ldots\ldots]$ denotes vector product. $\mathbf{n}_i$ is orthogonal to the plane of $\mathbf{C}_{i-1,i}$ and $\mathbf{C}_{i,i+1}$ (cf. the definition of the vector product) so it is also orthogonal to $\mathbf{h}_i$. Now, it is easily verified that if $\mathbf{r}_i$ and $\mathbf{s}_i$ are given by (7) and (8)

$$\mathbf{r}_i = d(\mathbf{h}_i \cos \gamma/2 + \mathbf{n}_i \sin \gamma/2) \tag{7}$$

$$\mathbf{s}_i = d(\mathbf{h}_i \cos \gamma/2 - \mathbf{n}_i \sin \gamma/2) \tag{8}$$

then all of the five relations given in (3) and (4) are identically satisfied. Thus having found the vectors corresponding to the C–C skeleton of the molecule, the molecular geometry (including all H . . . H distances) is completely solved.

For the solution of step (1) we can use the $n + 3$ relations ($n$ scalar and one vector equation) given in (1) and (2). We have $n$ unknown vectors of constant length ($c$), that is $2n$ unknowns. Hence conditions (1) and (2) alone are insufficient for determination of the conformation and we can obtain an unrestricted number of solutions. We may obtain a definite solution only if we introduce additional restrictions, e.g. caused by the presence of a certain symmetry. We shall confine ourselves to the latter case.

We can approach construction of the conformation by utilizing "building units" such as a triangle, one of whose angles is tetrahedral and a trapezoid with two tetrahedral angles. These units are suitably combined in accordance with the presumed properties of the conformation being considered. (See, for example, heavy bonds in cycloheptane chair conformation, Fig. 1.)

To illustrate the method which applies also to larger rings (step 1) we treat two specific cases in detail.

*Cycloheptane chair*

We assume a plane of symmetry which contains carbon atom 1 and the mid-point between carbon atoms 4 and 5 (Fig. 1). We label this as the $yz$ plane. Let carbon atoms 2, 3, 6, 7 be in the $xy$ plane. The distances 2–7 and 3–6 are given by the relations:

$$\overline{2\text{–}7} = 2c \sin \gamma/2 \qquad \overline{3\text{–}6} = c(1 + 2 \sin (\gamma - \pi/2)) \tag{9}$$
$$= \overline{2\text{–}7} + 2c \sin \delta$$

These ensure the validity of (2) for $i = 1$, 4 and 5. The plane of atoms 1, 2, 7 forms an angle $\phi$ with the $xy$ plane. This can be determined on the basis of the condition $(\mathbf{C}_{2,1}\mathbf{C}_{2,3}) = c^2 \cos\gamma = (\mathbf{C}_{7,1}\mathbf{C}_{7,6})$

$$\mathrm{Cos}\,\phi = -\frac{\cos\gamma + \sin\delta \sin\gamma/2}{\cos\delta \cos\gamma/2} \tag{10}$$

Analogously, the angle $\psi$ between the plane of atoms 3, 4, 5, 6 and the $xy$ plane is given on the basis of the condition

$$(\mathbf{C}_{3,2}\mathbf{C}_{3,4}) = c^2 \cos\gamma = (\mathbf{C}_{6,5}\mathbf{C}_{6,7})$$

$$\cos\psi = -\frac{\cos\gamma\,(1 + \sin\delta)}{\sin\gamma \cos\delta} \tag{11}$$

Having determined $\phi$ and $\psi$ we have completely fixed the C–C skeleton. From the method of construction of the $\mathbf{C}_{i,i+1} - s$ it is obvious that they also fulfil relation (1).

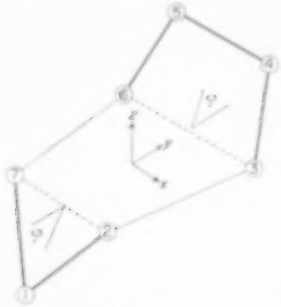


FIG. 1

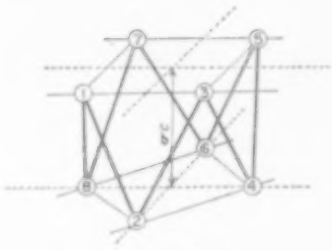


FIG. 2

From the above, the geometry of the boat conformation may be obtained simply by changing the sign of $\phi$.

$C_{2n}H_{4n}$ *with* n-*fold rotation symmetry*

We assume the molecule possesses an $n$-fold rotation axis (conveniently taken as the axis $z$), i.e. performing rotation through an angle $(2\pi/n)$ about the $z$ axis causes no change in the conformation. Examples are the cyclohexane chair conformation, cyclo-octane crown, cyclodecane crown, etc. Molecular symmetry permits determination of all interatomic distances very simply.

We place the atoms $C_1, C_3, \ldots, C_{2n-1}$ on the $n$ vertices of an equilateral polygon whose centre is on the $z$ axis and its plane parallel to the $xy$ plane. The atoms $C_2$, $C_4, \ldots\ldots C_{2n}$ are situated on the $n$ vertices of another equilateral polygon with the same centre, its plane parallel to the $xy$ plane, it being rotated through $\frac{1}{2}(2\pi/n) = \alpha$ with respect to the former polygon. (Cf. Fig. 2 for the cyclo-octane crown, $n = 4$; $\alpha = 45°$.)

The distance between the two planes ($bc$) and the radius of the polygons ($rc$) are determined on the basis of the condition

$$(\mathbf{C}_{i,i+1}\mathbf{C}_{i,i-1}) = c^2 \cos\gamma \tag{12}$$

The co-ordinates of the carbon atoms are given by

$$\mathbf{C}_{2i} = c\begin{cases} r\sin(2i)\alpha \\ r\cos(2i)\alpha \\ b \end{cases} \qquad \mathbf{C}_{2i+1} = c\begin{cases} r\sin(2i+1)\alpha \\ r\cos(2i+1)\alpha \\ 0 \end{cases} \tag{14}$$

The vectors connecting the carbon atoms are as follows:

$$\mathbf{C}_{2i-1,2i} = c\begin{cases} r_1\cos(2i-1/2)\alpha \\ r_1\sin(2i-1/2)\alpha \\ b \end{cases} \qquad \mathbf{C}_{2i,2i+1} = c\begin{cases} r_1\cos(2i+1/2)\alpha \\ r_1\sin(2i+1/2)\alpha \\ -b \end{cases} \tag{15}$$

$$r_1 = 2r\sin\alpha/2 \tag{16}$$

On the basis of (12) $b$ and $r_1$ are given as follows:

$$r_1^2 = \frac{1-\cos\gamma}{1+\cos\alpha} \tag{17}$$

$$b^2 = \frac{\cos\alpha+\cos\gamma}{1+\cos\alpha} \tag{18}$$

Having completely determined the C–C skeleton, we immediately obtain the vectors $\mathbf{r}_i$ and $\mathbf{s}_i$ and thence the positions and distances of the hydrogen atoms. The co-ordinates of the hydrogen atoms are given in Table 1, from which all H–H distances may be obtained.

TABLE 1

| | $H_{2i}$ axial | $H_{2i}$ equatorial | $H_{2i+1}$ equatorial | $H_{2i+1}$ axial |
|---|---|---|---|---|
| $x$ | $(e-f)\sin 2i\alpha$ | $(e+f)\sin 2i\alpha$ | $(e+f)\sin(2i+1)\alpha$ | $(e-f)\sin(2i+1)\alpha$ |
| $y$ | $(e-f)\cos 2i\alpha$ | $(e+f)\cos 2i\alpha$ | $(e+f)\cos(2i+1)\alpha$ | $(e-f)\cos(2i+1)\alpha$ |
| $z$ | $-g-h$ | $-g+h$ | $g-h$ | $g+h$ |

where, $e = r + \dfrac{d}{c}r_1\sin\alpha/2 \qquad g = 3/2\,b + b\dfrac{d}{c}$

$$f = \frac{dr_1 b}{C^2}\frac{\cos\alpha/2}{\cos\gamma/2} \qquad h = \frac{1}{2}\frac{dr_1^2\sin\alpha}{\cos\gamma/2} \tag{19}$$

*Cyclo alkenes.* The above treatment can be extended to cyclo-alkenes. The only difference is concerned with the bonds adjacent to the double bond. We must take into account:

(a) the length of the C=C bond, $c = 1{\cdot}334$ A°: the length of the C—H bond attached to the double bond $d = 1{\cdot}079$ A°.

(b) the valence angle 120°

(c) that the five vectors $\mathbf{C}_{i-1,i}$, $\mathbf{C}_{i,i+1}$, $\mathbf{C}_{i+1,i+2}$, $\mathbf{d}_i$ and $\mathbf{d}_{i+1}$ are in the same plane.

Having determined the C–C skeleton, the vectors pointing to the hydrogens adjacent to the double bond are given as follows:

$$\mathbf{d}_i = \frac{d'}{c}\mathbf{C}_{i-1,i} - \frac{d'}{c'}\mathbf{C}_{i,i+1} \qquad \mathbf{d}_{i+1} = \frac{d'}{c'}\mathbf{C}_{i+1} - \frac{d'}{c}\mathbf{C}_{i+1,i+2} \tag{20}$$

where $c$ = C–C single bond distance; $c'$ = C=C double bond distance; $d'$ = C–H bond distance for bond adjacent to double bond.

FIG. 3

*Energetic relations*

To compare the stability of different conformations of a given molecule we must relate their energies to their geometries.

There is a number of potential functions which have been put forward in order to represent the H . . . H non-bonded interaction.

Eyring[7] using the perfect pairing approximation, obtains the interaction energy of two non-bonded hydrogen atoms as follows:

$$E_{H,H} = Q_{H,H} - 1/2J_{H,H}$$

where $Q$ and $J$ are the coulomb and exchange integrals. This corresponds[8] to the interaction of two H atoms with random spin orientation, which in turn can be expressed as:

$$1/4\, f(^1\Sigma) + 3/4\, f(^3\Sigma)$$

where $f(^1\Sigma)$ and $f(^3\Sigma)$ are the interaction energies of two hydrogen atoms in the bonding singlet and in the repulsive triplet states, respectively.

This function has the disadvantage that it predicts only 0·4 kcal/mole for the potential barrier in ethane (experimental value about 3 kcal/mole). Barton[9] used a van der Waals interaction type function which also yielded too small values for the potential barrier in ethane. The function he employed contains the van der Waals radius of H which is not defined exactly. Mason and Kreevoy[10] suggested that the appropriate potential function could be represented by the function $Kf(^3\Sigma)$ where $K$ is a numerical constant. The Eyring potential corresponds to a value $\frac{1}{3}$–$\frac{1}{2}$. Pritchard and Sumner[11] used the value $K = 0{\cdot}5$. Mason and Kreevoy suggested $K = 1$ and using this value obtained a better agreement with the experiment for the potential barrier in ethane. This value was used by Howlett[12] who corrected for the angular dependence.

[7] H. Eyring, *J. Amer. Chem. Soc.* **54**, 3191 (1932).
[8] C. A. Coulson, *Valence* pp. 167–168. Clarendon Press, Oxford (1952).
[9] D. H. R. Barton, *J. Chem. Soc.* 340 (1948).
[10] E. A. Mason and M. M. Kreevoy, *J. Amer. Chem. Soc.* **77**, 5808 (1955).
[11] H. O. Pritchard and F. H. Sumner, *J. Chem. Soc.* 1041 (1955).
[12] K. E. Howlett, *J. Chem. Soc.* 4353 (1957).

We wish to compare the stabilities of some conformations. In view of the large uncertainty in the choice of the correct potential function we cannot hope to obtain correct figures for the interaction energies. We adopt the following potential function $0{\cdot}5\,f(^3\Sigma)$, i.e. that used by Pritchard and Sumner. $f(^3\Sigma)$ is given by the approximation formula of Buckingham[13] which agrees reasonably well with the values obtained from theoretical calculations.[14]

$$f(R) = \frac{627{\cdot}211}{R}\{1 + 1{\cdot}167R + 0{\cdot}039R^2 + 0{\cdot}518R^3 + 0{\cdot}864R^4\}\exp.(-2{\cdot}3R) \quad (21)$$

$R$ in atomic units (the unit of length $a_0 = 0{\cdot}5292$ A°), $f(R)$ in kcal/mole.

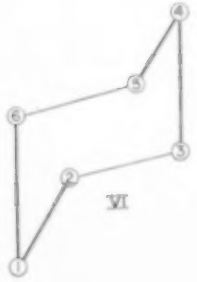
We have determined the geometry of some conformations. Summing over all of the H . . . H interactions, we obtain the results summarized in Table 2.

TABLE 2. ENERGY GIVEN IN kcal/mole

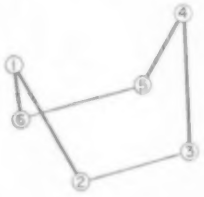
| Energy | | Energy | | Energy | | Energy | | Energy | |
|---|---|---|---|---|---|---|---|---|---|
| VI | 15·70 | X | 66·34 | XIV | 191·52 | XVIII | 48·52 | XXII | 18·60 |
| VII | 20·13 | XI | 107·19 | XV | 56·56 | XIX | 48·84 | XXIII | 31·51 |
| VIII | 42·03 | XII | 38·26 | XVI | 16·10 | XX | 61·10 | | |
| IX | 44·78 | XIII | 67·30 | XVII | 15·97 | XXI | 18·10 | | |

*Discussion of results*

*Cyclohexane* (VI, VII). We obtain a difference of 4·43 kcal/mole between the energies of the two conformations (Table 2), the chair (VI) being the more stable. This conclusion is in accord with the experimental findings and yields the same order of magnitude as alternative methods for estimating the energy difference.[15]



VI



VII

*Cycloheptane* (VIII, IX). Once again the chair conformation (VIII) is the more stable by 2·75 kcal/mole. We must note, however, that the 3–6 interaction is extremely high, due to the fact that the 3a–6a distance is only 1·288 A°, corresponding

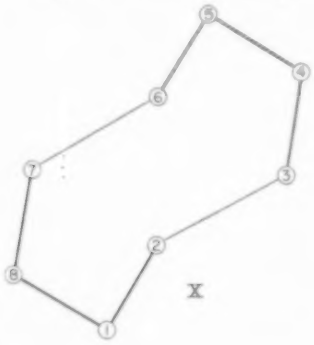
[13] R. A. Buckingham, *Trans. Faraday Soc.* **54**, 453 (1958).
[14] J. O. Hirschfelder and J. W. Linnett, *J. Chem. Phys.* **18**, 130 (1950); H. M. James, A. S. Coolidge and R. D. Present, *J. Chem. Phys.* **4**, 187 (1936).
[15] C. W. Beckett, K. S. Pitzer and R. Spitzer, *J. Amer. Chem. Soc.* **69**, 2488 (1947).

to a repulsion energy of 20·01 kcal/mole. It is very improbable that this distance remains unaltered in the real molecule. There must be deformations from the "ideal" structure causing deviations from the strictly tetrahedral bond angles (see below).

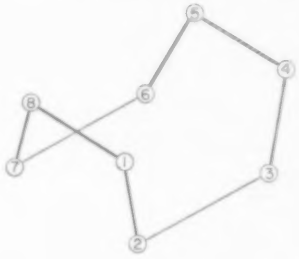
VIII

IX

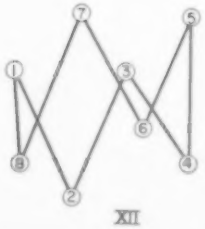
*Cyclo-octane* (X–XIV). The most stable conformation among the "ideal" structures is the crown form XII (Table 4). However, this conclusion depends largely upon the fact that high repulsions occur in the chair (X) and in the boat (XI) forms (the 2a–7a and 3a–6a H–H distances in X and the 2a–7a, 3a–6a, 1a–4a and 5a–8a H–H distances in XI are all 1·265 A°. This value corresponds to an energy value of 21·11 kcal/mole. Even higher repulsions occur in conformations XIII and XIV. As we have noted above, such small distances are extremely unlikely to obtain in the real molecule and we must consider possible deformations.




X




XI




XII

*Cyclodecane* (XV). In view of the extremely high number of possible conformations it seemed pointless to extend the calculations beyond cyclo-octane. However, the cyclodecane crown form XV is given because its comparison with the cyclo-octane

XIII

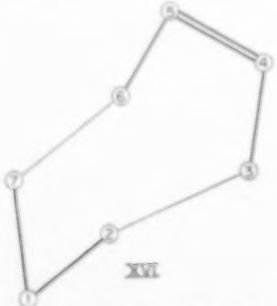
XIV

brown form XII is illuminating. The most striking feature of the comparison is the use of the second neighbour interaction (1–3): in XII it is 2·85 kcal/mole; in XV it is 3·74 kcal/mole. This corresponds to the shortening of the la–3a H–H distances: 2·018 A° and 1·924 A°, respectively. This indicates the improbability of the crown form remaining the most stable one in the larger rings.

XV

It is clear that both in cyclononane and in cyclodecane the higher flexibility of the molecule makes it more difficult to assign the values for the 1,5 and 1,6 H . . . H non-bonded interactions albeit these values must be relatively high in the transition states for transannular reactions. It is hoped that more light will be shed on this point by our new approach (see below).

*Cycloheptene* (XVI, XVII). In contrast with the preceding results for cycloheptane, the boat form XVII is the more stable by a value of 0·67 kcal/mole. In this molecule the high 3–6 repulsions present in the saturated compound disappear. With the opening of the valency angle at $C_4$ and $C_5$ from the tetrahedral to 120°, the 3a–6a distance becomes 2·108 A°, corresponding to 2·12 kcal/mole only. We note that this distance is very sensitive to the valency angle at $C_4$ and $C_5$.



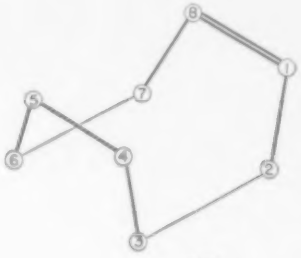
XVI

XVII

*Cyclo-octene* (XVIII–XX). Once again the boat form XIX is more stable but the difference is extremely small, 0·31 kcal/mole. However, we have large repulsions

(28·43 kcal/mole) both in XVIII and in XIX, indicating the necessity of altering the situation through small deformations. The same conclusion holds for the skew form XX.

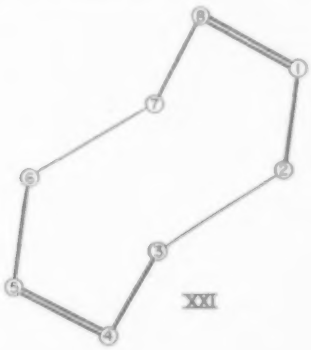
XVIII



XIX

XX

1,5-*Cyclo-octadiene* (XXI–XXIII). Here again we find that the boat form XXII is more stable, the difference being 0·51 kcal/mole. This conclusion is firmer than that for cyclo-octene as here we do not have high repulsions. The skew form XXIII is less stable than either the boat or the chair XXI form.

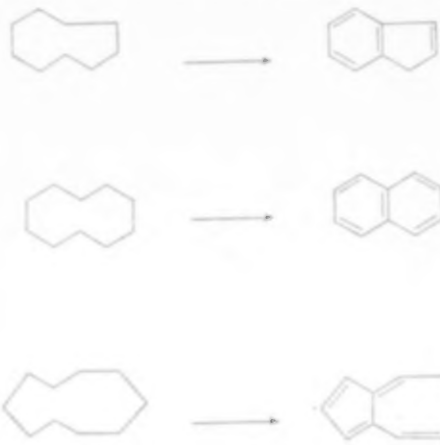


XXI

XXII

XXIII

The formation of indane by dehydrogenation of cyclononane with palladized charcoal and the formation of naphthalene or azulene by similar treatment of cyclodecane[16] makes certain conformations of the cyclo-alkanes appear particularly attractive. However, both the fact that the reactions are carried out at 400° and the high H–H



interaction energies between the 1,5 and the 1,6 positions make such an assumption appear as an oversimplification. So would also appear an explanation such as given for ring cleavage of cyclononyl acetate at 500° to yield 1,8-nonadiene via a 1,4-transannular elimination.[17]

Conformation XIV for cyclo-octane was taken as a model calculation for a case in which 1,5-transannular reaction may take place. If we apply the assumption used throughout, namely that the H–H interaction is the same as the repulsive interaction of the hydrogen atoms in the anti-bonding state, multiplied by a factor of $\frac{1}{2}$, we obtain an enormous repulsion energy for the 1,5-hydrogens (160 kcal/mole). Yet the formation of XXX from XXIX by 1,5-transannular interaction followed by dehydration, does take place.[18]

Many further examples of transannular interactions are known to occur.[19]

From this it follows that in the above and in analogous cases we may reasonably assume that deformations from the "ideal" more symmetrical conformations, as exemplified above, must in fact occur. This would permit decrease of repulsions at various points in the molecule whilst still permitting the formation of the transition state required for driving these transannular reactions to their respective goals.

[16] V. Prelog, V. Boarland and S. Polyak, *Helv. Chim. Acta* **38**, 434 (1955).
[17] A. T. Blomquist and P. R. Taussig, *J. Amer. Chem. Soc.* **77**, 6399 (1955).
[18] A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Amer. Chem. Soc.* **74**, 5884 (1952); A. C. Cope and W. R. Schmitz, *Ibid.* **72**, 3056 (1950).
[19] *Inter alia*, A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Amer. Chem. Soc.* **79**, 3905 (1957) and many preceding papers; A. T. Blomquist and P. R. Taussig, *Ibid.* **79**, 3505 (1957) and many preceding papers; V. Prelog and W. Küng, *Helv. Chim. Acta* **39**, 1394 (1956) and many preceding papers.

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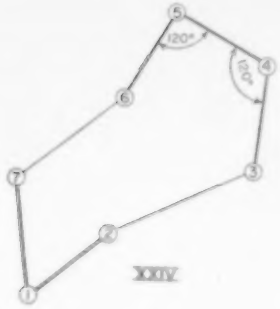
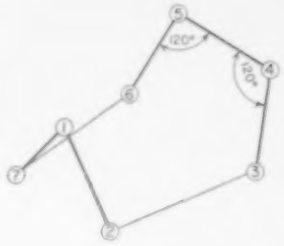
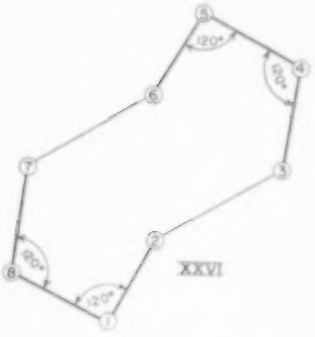


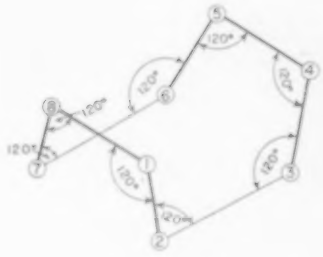

XXIV




XXV




XXVI




XXVII

XXIX XXX

Indeed, Dunitz's recent X-ray diffraction measurements show that there are considerable deviations from tetrahedral angles in the carbon skeleton of certain cyclononane,[20] cyclodecane,[21] and cyclododecane derivatives.[22,23]

We therefore turn to a short discussion of the effect of introducing certain deformations into some of the above more idealized conformations.

*Deformations*

Barton[9] noted in his early calculations on cyclohexane that the results largely depend upon a few small interatomic distances and that the molecule would probably gain stability by undergoing deformations which alter these distances. The deformations can occur variously. If we alter the skeletal bond angles the energy rises but concurrently there is a great decrease in the H . . . H non-bonded interaction. Little experimental data are available for the variation of the energy with the skeletal bond

[20] R. F. Bryan and J. D. Dunitz, unpublished work.
[21] E. Buser and J. D. Dunitz, unpublished work.
[22] J. D. Dunitz and H. M. M. Shearer, *Proc. Chem. Soc.* 348 (1958).
[23] We gratefully acknowledge private communications from Professors Dunitz and Prelog on this point. Prof. Prelog has disclosed results leading to the formulation of the cyclodecane conformation at the Colloque International de Stereochemic at Montpellier on Sept. 8, 1959.

angle. Evans,[24] using thermochemical data and force constants, estimates the energy required to decrease the skeletal angle from the tetrahedral value by 5°, 10° and 20° to be only 0·4, 1·8 and 7 kcal/mole, respectively. Assuming that the same figures apply to the increase in bond angles, then an increase of 11° raises the energy by about 2 kcal/mole. At the same time the greatest H . . . H interactions drop very sharply by about 20 kcal/mole. Table 3 summarizes calculations in which we have used this deformation for cycloheptane and cyclo-octane.

TABLE 3

| Interaction energy | | Energy of deformation (kcal/mole) |
|---|---|---|
| XXIV | 24·87 | 4 |
| XXV | 33·00 | 4 |
| XXVI | 32·72 | 8 |
| XXVII | 32·93 | 16 |

We see that for cycloheptane it is again predicted that the chair form is the more stable, the energy difference being increased to 8·13 kcal/mole. For cyclo-octane the energies are in the same range as for the crown form, the chair (with deformation) being the most stable.

In the preceding illustrative calculations we changed only those angles (while preserving the symmetry of the conformation) which affect mostly the shortest H . . . H distances. Evidently a more thorough treatment is needed which allows for the variations of all of the angles and takes into account unsymmetrical conformations too. However this exceeds the scope of this simple method which is suitable only for preliminary information regarding the geometry of the molecule. We intend to return to this problem using a more general method which was applied by Lifson[25] to a study of long chain polymer structures. Use of the electronic computer facilities (Weizac) of the Weizmann Institute of Science permits introduction of changes in a number of conformational parameters simultaneously. The results will be reported in a subsequent paper.[26]

Tables of distances between non-bonded hydrogens and their interaction energies for the various conformations discussed above may be obtained from the authors.

*Acknowledgement*—One of us (D. G.) is grateful of Prof. V. Prelog for stimulating discussions.

[24] A. C. Evans, *Trans. Faraday Soc.* **42**, 719 (1946).
[25] S. Lifson, *J. Chem. Phys.* **29**, 80, 89 (1958); **30**, 964 (1959).
[26] S. Lifson, R. Pauncz and D. Ginsburg, to be published.

Tetrahedron, 1960, Vol. 9, pp. 53 to 57. Pergamon Press Ltd. Printed in Northern Ireland

# CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—III

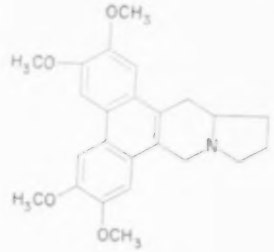
## THE COMPLETE STRUCTURE OF TYLOPHORINE

T. R. GOVINDACHARI, M. V. LAKSHMIKANTHAM, B. R. PAI and S. RAJAPPA
Department of Chemistry, Presidency College, Madras

(*Received* 2 *October* 1959)

**Abstract**—2,3,6,7-Tetramethoxyphenanthrene-9,10-dicarboxylimide has been synthesized and proved to be identical with the oxidation product of tylophorine isomethohydroxide, confirming the previous formulation of tylophorine as 2,3,6,7-tetramethoxyphenanthro (9,10,6′,7′)-indolizidine. Some further interesting degradation reactions on tylophorine have been carried out.

THE alkaloid tylophorine[2] had been assigned structure I on the basis of degradation evidence presented in a previous communication.[1] Although one point of fusion of the heterobicyclic system was conclusively shown to be the 9- position of the phenanthrene ring, the location of the second point of fusion as the 10- position was based on biogenetic considerations and the incompatibility of the degradation results with fusion at the 8,9- position.




I

Definite evidence is now presented, which proves that the fusion of the indolizidine ring is indeed at the 9,10- position as in structure I.

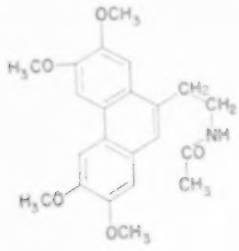
On submitting tylophorine to zinc dust distillation, a compound, m.p. 135–137°, was obtained. This had absorption maxima in the ultra-violet identical with that of 9,10-dimethylphenanthrene and its melting point was not depressed on admixture with the latter (m.p. 144°).

Oxidation of isodihydrohomotylophorinemethine[1] had yielded a dicarboxylic acid considered to be 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylic acid. Attempts to confirm this structure by preparing this compound by oxidation of the methyl groups in 2,3,6,7-tetramethoxy-9,10-dimethylphenanthrene, obtained by the Clemmensen reduction[3] of 2,2′-diacetyl-4,5,4′,5′-tetramethoxydiphenyl, were all unsuccessful.

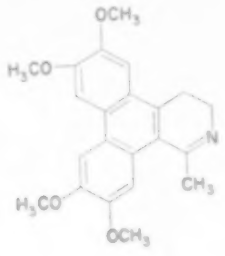
It had been reported[1] that oxidation of tylophorine isomethohydroxide yielded

[1] Part II, T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958).
[2] T. R. Govindachari, B. R. Pai and K. Nagarajan, *J. Chem. Soc.* 2801 (1954).
[3] D. M. Hall, J. E. Ladbury, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* 3475 (1956).

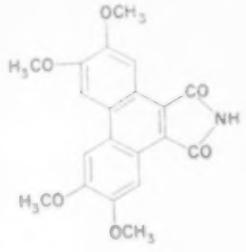
an imide considered to be 2,3,6,7-tetramethoxy-9,10-dicarboxylimide. This has now been confirmed by the following synthesis, which therefore provides conclusive proof about the positions of fusion of the indolizidine system to the phenanthrene ring. Condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde[1] with nitromethane yielded the corresponding 9-2′-nitrovinylphenanthrene, which was reduced by lithium aluminium hydride to 2,3,6,7-tetramethoxy-9-2′-aminoethylphenanthrene, characterized as the acetyl derivative II. Cyclization with phosphorus oxychloride gave the




II




III




IV

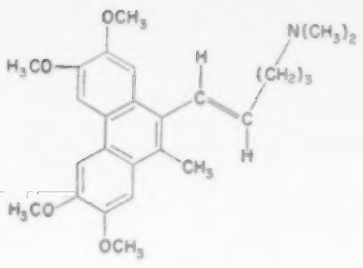
dihydroisoquinoline (III), whose methiodide on oxidation with aqueous potassium permanganate yielded 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylimide (IV), identical in all respects (mixed m.p. infra-red and ultra-violet absorption spectra) with the oxidation product from tylophorine.

A study of the Hofmann and Emde degradations applied to tylophorine has brought to light certain interesting features. It is found that Emde degradation of tylophorine methiodide yields a product identical with that obtained from tylophorine isomethiodide.[1] Evidently, conversion to the *iso* compound precedes bond cleavage.[4] When tylophorinemethine[1] is submitted to an Emde degradation, a compound $C_{26}H_{33}O_4N$, m.p. 155–156°, is obtained, isomeric and not identical with isodihydrohomotylophorinemethine,[1] m.p. 142°, reported earlier. Apparently, in the present case, during the Emde degradation, reductive cleavage of a —C—N— bond has occurred, but not reduction of the double bond present in the methine.

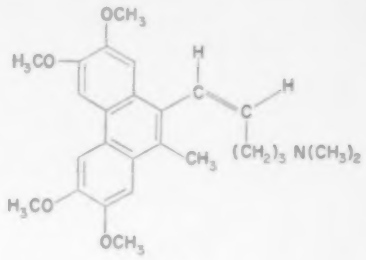
The compounds m.p. 155–156° and m.p. 142° have almost identical infra-red spectra, except that the latter has a strong band at 10·23 $\mu$ absent in the former, and in the common product, tetrahydrohomotylophorinemethine, m.p. 138–140°, obtained by catalytic reduction of either compound. It is evident that the two compounds are geometrical isomers, the compound m.p. 142°, being the *trans* (V) and the compound m.p. 155–156° being the cis (VI) isomers.

When tylophorine methiodide is subjected to Hofmann degradation, the double bond formed in the elimination reaction is likely to have the less strained *cis*- configuration, since it would have to form part of a nine-membered ring (VII).[5] When isodihydrohomotylophorine methiodide (VIII) is subjected to a Hofmann degradation, no such restriction is present and the more stable *trans*- isomer results, as borne out by the infra-red spectrum showing a strong band at 10·23 $\mu$, characteristic of a *trans*- disubstituted ethylenic linkage.[6]

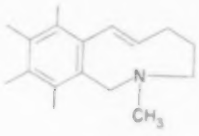
[4] E. Gellert, *Aust. J. Chem.* **9**, 489 (1956).
[5] A *trans* double bond in a 9-membered ring is known to be strained. A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Amer. Chem. Soc.* **74**, 3643 (1952).
[6] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 31. Methuen, London (1954).



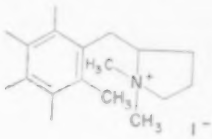
V



VI



VII



VIII

## EXPERIMENTAL

*Zinc dust distillation of tylophorine*

Tylophorine (50 mg) was intimately mixed with zinc dust (B.D.H. Analar grade; 5 g) and heated in a Pyrex tube at 450–500° in a current of dry, oxygen-free nitrogen for 45 min. The tube was then cooled, the zinc tapped off, and the distillate washed into a flask with ether and alcohol. Twenty such batches were run and the collected distillate sublimed at 160–180°/2 × $10^{-3}$ mm. The sublimate was crystallized twice from alcohol to give a product (<1 mg), m.p. 135–137° after slight sintering at 130°. The m.p. was unaffected on admixture with authentic 9,10-dimethylphenanthrene[3] (m.p. 144°). Both the compounds had $\lambda_{max}$ 255, 300, 335, 352 mμ (there being insufficient material for determination of $\varepsilon_{max}$).

2,3,6,7-*Tetramethoxy*-9,10-*dimethylphenanthrene*

(a) 2,2′-*Diacetyl*-4,5,4′,5′-*tetramethoxydiphenyl*. 6-Aminoacetoveratrone[7] (5 g) dissolved in dil HCl (40 ml; 4N) was diazotized at 0° with aqueous sodium nitrite solution (1·8 g in 5 ml), added dropwise with stirring. Ice-cold hydroxylamine solution (from 2·2 g hydroxylamine hydrochloride in 6 ml water and 5·1 ml 4N NaOH) was added with stirring to the cuprammonium solution obtained by treatment of aqueous copper sulphate solution (7·5 g in 25 ml) with liquid ammonia (10·2 ml) at 0°. To this reducing solution was added the diazo solution dropwise with stirring at 10° and left at 30° till the evolution of nitrogen ceased. The solid was filtered, washed with water, dried and then recrystallized from ethanol containing acetic acid to give 2,2′-*diacetyl*-4,5,4′,5′-*tetramethoxydiphenyl* (3 g), m.p. 212°. (Found: C, 67·2; H, 6·3. $C_{20}H_{22}O_6$ requires: C, 67·0; H, 6·1%.).

(b) 2,3,6,7-*Tetramethoxy*-9,10-*dimethylphenanthrene*. A mixture of the foregoing diketone (4 g), amalgamated zinc (40 g), ethanol (100 ml) and conc HCl (50 ml) was refluxed for 4 hr. The organic matter was extracted with chloroform, washed with water, dried ($Na_2SO_4$) and distilled. The residue was recrystallized from alcohol to give the pure *dimethylphenanthrene* (1·2 g), m.p. 225°; $\lambda_{max}$ 255, 290, 340, 355 mμ (log ε 4·80, 4·54, 3·06, 2·64) (Found: C, 73·3; H, 6·8. $C_{20}H_{22}O_4$ requires: C, 73·6; H, 6·7%).

2,3,6,7-*Tetramethoxyphenanthrene*-9,10-*dicarboxylimide*

(a) 2,3,6,7-*Tetramethoxy*-9-2′-*nitrovinylphenanthrene*. A mixture of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde[1] (1·5 g) nitromethane (8 ml), ammonium acetate (1·5 g) and glacial acetic acid (10 ml) was refluxed for 2 hr and poured into water. The solid was filtered, washed and dried. Recrystallization from acetic acid gave the pure *nitrostyrene* (1·2 g), m.p. 250° (decomp) (Found: C, 64·7; H, 5·4. $C_{20}H_{19}O_6N$ requires: C, 65·0; H, 5·2%).

[7] J. C. E. Simpson, C. M. Atkinson, K. Schofield, and O. Stephenson, *J. Chem. Soc.* 646 (1945).

(b) 2,3,6,7-*Tetramethoxy*-9-2′-*acetamidoethylphenanthrene*. The foregoing nitrostyrene (1·4 g) was added gradually with stirring to a suspension of lithium aluminium hydride (1·5 g) in dry tetrahydrofuran (150 ml) at 30°. After several hours, the mixture was decomposed by the addition of moist ether (150 ml) followed by water. The solvent mixture was separated, dried and the solvents removed to give the crude basic material (1·4 g). This could not be purified and was acetylated by refluxing with acetic anhydride (5 ml) and fused sodium acetate (0·5 g) for 1 hr. The acetyl derivative was extracted with chloroform, dried and distilled. The residue (1·6 g) on recrystallization from alcohol gave the *acetyl derivative* (0·8 g), m.p. 190° (Found: C, 66·9, 67·1, 67·4; H, 6·8, 7·0, 6·8. $C_{22}H_{25}O_5N \cdot \frac{1}{2}H_2O$ requires: C, 67·4; H, 6·6%).

(c) *The Dihydroisoquinoline* (III). The acetyl derivative (0·4 g) was refluxed with phosphorus oxychloride (6 ml) for 1 hr, and then poured on crushed ice. After removal of the non-basic material by extraction with benzene, the solution was cooled, basified with ammonia and extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous potassium carbonate. Removal of the solvent gave the free base (0·25 g) which was chromagraphed in benzene solution on alumina, the base being eluted with benzene containing alcohol (1%). The solid obtained on evaporation of the eluate was recrystallized from methanol to give the *dihydroisoquinoline*, m.p. 180° (Found: C, 71·9; H, 6·5. $C_{23}H_{23}O_4N$ requires: C, 72·3; H, 6·3%). The *picrate* made by mixing alcoholic solutions of the base and picric acid, was recrystallized from acetic acid and had m.p. 245° (decomp) (Found: C, 56·9; H, 4·6. $C_{29}H_{26}O_{11}N_4$ requires: C, 56·6; H, 4·4%).

(d) 2,3,6,7-*Tetramethoxyphenanthrene*-9,10-*dicarboxylimide*. The foregoing dihydroisoquinoline was converted to the methiodide by refluxing with methyl iodide in chloroform solution. The methiodide (0·25 g) in water (70 ml) was treated at 30° with aqueous potassium permanganate solution (0·5 g in 70 ml) added dropwise with stirring. The mixture was left overnight, then treated with excess sulphurous acid and exhaustively extracted with chloroform. The combined chloroform extracts were washed with water and dried over anhydrous magnesium sulphate. The solvent was removed and the residue filtered in fresh chloroform solution through a short column of alumina. The solid obtained by evaporation of the eluate was recrystallized from pyridine to give the *imide*, m.p. 355° (decomp) with shrinking above 330°, identical (m.p. and Infra-red) with that obtained by the oxidation of tylophorine isomethohydroxide[1] (Found: C, 65·2; H, 4·5. Calc. for $C_{20}H_{17}O_6N$: C, 65·4; H, 4·6%).

*Emde degradation of tylophorine*.

Tylophorine methiodide (0·25 g) was refluxed with silver chloride (from 1 g silver nitrate) in water (10 ml) and alcohol (10 ml) for 5 hr, and left overnight. The mixture was filtered, and the alcohol distilled off. The aqueous solution of the methochloride was treated with sodium amalgam (5%; 25 g) at 100° and left overnight. The solid which had separated was extracted with benzene, dried and distilled. The residual solid (75 mg) was crystallized from benzene–petroleum ether (b.p. 40–60°) to give the Emde base, m.p. and mixed m.p. with isodihydrohomotylophorine[1], 200–202°, $[\alpha]_D^{20} \pm 0°$.

*Emde degradation of tylophorinemethine*

Tylophorinemethine methiodide[2] (0·9 g) was converted to the methochloride by refluxing with silver chloride (from 3 g silver nitrate) in water (20 ml) and alcohol (20 ml) for 4 hr, filtering and evaporating the alcohol. The aqueous solution of the methochloride (100 ml) was treated with sodium amalgam (5%; 100 g) at 100° over 3 hr. Heating was continued for 3 more hr and left overnight at 30°. After decanting from the mercury, the mixture was repeatedly extracted with ether, the ether solution dried and distilled, leaving behind a white solid (0·4 g), m.p. 155–156° (from ether), not identical with isodihydrohomotylophorinemethine[1] (m.p. 142°) (Found: C, 73·8; H, 7·9. $C_{24}H_{33}O_4N$ requires: C, 73·8; H, 7·8%). $\lambda_{max}$ 258, 288, 340, 355 m$\mu$ (log $\varepsilon$ 4·84, 4·66, 3·19, 2·89).

*Catalytic reduction of the Hofmann-Emde base*

The above base (100 mg) in water (10 ml) containing 4 N HCl (2 ml) was hydrogenated at 50 lbs/in$^2$ in presence of Adams catalyst (50 mg) for 3 hr. The solution was then filtered, basified with ammonia and extracted with ether. The residue (100 mg) after evaporation of the ether was recrystallized from dry ether to give *tetrahydrohomotylophorinemethine*, m.p. 138–140°. On admixture with the starting

material, (m.p. 155–156°), it melted at 134–135°; on admixture with isodihydrohomotylophorinemethine (m.p. 142°) it had m.p. 130–134°. (Found: C, 73·2; H, 8·1. $C_{24}H_{33}O_4N$ requires: C,73·4; H, 8·2%). $\lambda_{max}$ 255, 290, 340, 355 m$\mu$ (log $\varepsilon$ 4·73, 4·48, 3·03, 2·55).

*Catalytic reduction of isodihydrohomotylophorinemethine*

Isodihydrohomotylophorinemethine (100 mg) was reduced as before, to give a product (100 mg), identical with tetrahydrohomotylophorinemethine (m.p., mixed m.p. and infra-red) (Found: C, 73·6; H, 8·3%).

VOL. 9 1960

*Acknowledgement*—We are grateful to Dr. K. Nagarajan for many valuable discussions, to Prof. C. L. Stevens for some of the infra-red spectra, and to Mr. S. Selvavinayakam for the microanalyses. We thank the Government of India for the award of a National Research Fellowship (to M. V. L.) and the Council of Scientific and Industrial Research for a Senior Research Fellowship (to S. R.) and a maintenance grant.

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# THE REACTION OF 2,4-DINITROBENZENESULPHENYL CHLORIDE WITH ORGANIC MONOSULPHIDES

C. G. MOORE and M. PORTER
The British Rubber Producers' Research Association, Welwyn Garden City, Herts

(*Received* 27 *October* 1959)

**Abstract**—2,4-Dinitrobenzenesulphenyl chloride (I) reacts with dialkyl, diaralkyl, and alkyl aralkyl monosulphides at ca. 20° in dry acetic acid to give alkyl or aralkyl 2,4-dinitrophenyl disulphides together with alkyl or aralkyl chlorides as major products. The reactivity order with respect to the constitution of the sulphide is: tertiary alkyl > benzyl > secondary alkyl > primary alkyl. With unsymmetrical sulphides, the more branched alkyl group is displaced by the 2,4-dinitrophenylthio group. Monosulphides containing allylically-unsaturated groups react with I both by its addition to the double bond and by fission of a C–S bond in the derived adduct. Based on the response of both the course and rate of reaction to the constitution of the monosulphide and to the nature of the solvent a polar mechanism is proposed, involving an initial electrophilic attack of the sulphenyl chloride on the sulphide sulphur to give a "sulphonium ion" type intermediate which then undergoes cleavage of a preferred C–S bond (dependent on the structures of the alkyl and aralkyl groups) to give the observed products.

AN exchange reaction of arenesulphenyl chlorides with organic disulphides which conforms closely to the stoicheiometry of reaction (1) has been reported recently:[1]

$$ArSCl + RS\text{-}SR \rightleftharpoons ArS\text{-}SR + RSCl \qquad (1)$$

The reaction of 2,4-dinitrobenzenesulphenyl chloride (I) with variously constituted saturated and allylically-unsaturated monosulphides is now described.

This work was undertaken in order to establish a chemical method for determining the amount of olefinic unsaturation in the mono- and polysulphides derived from sulphur-olefin interaction;[2] the principle is to react the unsaturated sulphidic mixture with a known excess of sulphenyl chloride in anhydrous acetic acid under conditions established as leading to quantitative addition of the reagent to olefins[3] and then to determine the unreacted sulphenyl chloride by an iodometric method based on that of Kharasch and Wald.[4] The exchange reaction (1) with disulphides present, and comparable reactions with higher polysulphides, would not interfere since sulphenyl chloride function is not lost in these processes.[1] However, when the method was applied to authentic alkenyl alkyl monosulphides (viz., $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}Bu^t$ and $Me_2C{:}CH{\cdot}CH(Me){\cdot}S{\cdot}CH_2Ph$) considerably more than one molar equivalent of the sulphenyl chloride (I) was consumed (see Table), and this finding was followed by the observation that saturated monosulphides also react with I, thus rendering the method invalid.

It has now been established (see Table) that reaction between I and dialkyl,

[1] C. G. Moore and M. Porter, *J. Chem. Soc.* 2890 (1958).
[2] L. Bateman, C. G. Moore and M. Porter, *J. Chem. Soc.* 2866 (1958).
[3] N. Kharasch, H. L. Wehrmeister and H. Tigerman, *J. Amer. Chem. Soc.* **69**, 1612 (1947); W. L. Orr and N. Kharasch, *Ibid.* **75**, 6030 (1953); and other papers in the same series.
[4] N. Kharasch and M. M. Wald, *Analyt. Chem.* **27**, 996 (1955).

diaralkyl, and cyclic monosulphides is a general one, proceeding according to reaction (2) (Ar = 2,4-dinitrophenyl, here and throughout):

$$\underset{\text{I}}{\text{ArSCl}} + \underset{\text{II}}{\text{R·S·R}} \xrightarrow[20°]{\text{AcOH}} \text{ArS·SR} + \text{RCl} \qquad (2)$$

with the proviso that in some cases elimination of the group R to give olefin and hydrogen chloride, and acetolysis of RCl may be minor competing reactions.

REACTION OF 2,4-DINITROBENZENESULPHENYL CHLORIDE (I) WITH MONOSULPHIDES IN ACETIC ACID AT ca. 20°.

| Sulphide | Reaction time (hr) | Moles I consumed per mole of sulphide |
|---|---|---|
| Allyl t-butyl | 24·0 | 1·13 |
| | 168·0 | 1·31 |
| Benzyl 4-methylpent-3-en-2-yl | 23·5 | 1·66 |
| | 48·0 | 1·82 |
| | 119·0 | 1·97 |
| Di-n-propyl | 140·0 | 0·057 |
| Di-isopropyl | 65·5 | 0·072 |
| | 259·0 | 0·156 |
| | 523·0 | 0·276 |
| Isopropyl t-butyl | 17·0 | 1·02 |
| | 89·0 | 1·04 |
| Cyclohexyl methyl | 25·0 | 0·041 |
| | 47·0 | 0·264 |
| Diphenyl | 97·5 | 0·00 |
| | 288·0 | 0·00 |
| Dibenzyl | 21·5 | 0·251 |
| | 165·5 | 0·746 |
| Benzyl 2-methylpent-2-yl | 25·0 | 1·13 |
| | 122·5 | 1·20 |
| 2-Ethyl-5-isopropyl-2-methylthiacyclopentane | 22·0 | 0·670 |
| | 50·0 | 0·911 |

The validity of reaction (2) was shown in the case of II (R = $CH_2Ph$) by allowing equimolar quantities of I and dibenzyl sulphide to react in dry acetic acid at ca. 20°, when benzyl 2,4-dinitrophenyl disulphide was isolated (48 per cent yield after 48 hr reaction), and benzyl chloride, identified as S-benzylisothiuronium picrate (59 per cent yield after 283 hr reaction), was formed. The analogous reaction of I with II (R = isopropyl) gave 2,4-dinitrophenyl isopropyl disulphide (86 per cent yield after 529 hr at ca. 20° and 209 hr at 50°) and there was evidence for the presence of ca. 8 per cent of 2-chloropropyl 2′,4′-dinitrophenyl sulphide, presumably formed by the addition of I to propene,[5] the latter being derived from the displaced isopropyl group in II (R = isopropyl). The fact that monosulphides containing a tertiary alkyl group (e.g. benzyl 2-methylpent-2-yl sulphide) react with more than one molar equivalent of I (see Table) is similarly ascribed to the formation of olefin from the displaced

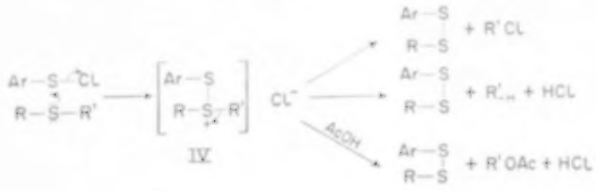
[5] N. Kharasch and C. M. Buess, *J. Amer. Chem. Soc.* **71**, 2724 (1949).

tertiary alkyl group in the primary reaction and subsequent addition of I to the olefin to give a chloroalkyl 2,4-dinitrophenyl sulphide.

In the reaction of I with unsymmetrical monosulphides III (reaction 3), the group R′ displaced as the chloride is that containing the more substituted α-carbon atom; thus, isopropyl t-butyl sulphide gives 2,4-dinitrophenyl isopropyl disulphide, and benzyl 2-methylpent-2-yl sulphide gives benzyl 2,4-dinitrophenyl disulphide. The

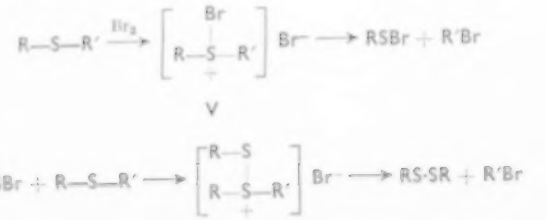
$$\underset{\text{I}}{\text{ArSCl}} + \underset{\text{III}}{\text{R·S·R′}} \rightarrow \text{ArS·SR} + \text{R′Cl} \qquad (3)$$

reaction rate also is markedly dependent on the structure of the saturated monosulphide, the rate increasing with increasing branching on the α-carbon atoms in R- and R′- (see Table). The course and rate of reaction appear, therefore, to depend upon the ease with which the groups R- and R′- in II and III are displaced as carbonium ions, the observed order (see Table) being: $Alk_3C- > PhCH_2- > Alk_2CH- > AlkCH_2- \gg Ph-$ (cf.[6]). These findings, coupled with the fact that the reaction of I with II (R = $CH_2Ph$) is slower in benzene than in acetic acid (see Experimental), suggest that reactions (2) and (3) involve a bimolecular electrophilic attack of the sulphenyl halide on the monosulphide to give a "sulphonium ion" type complex (IV) from which elimination of the cationically most stable group, R′-, occurs to give the observed products (reactions 4, 5, and 6):




(4) (5) (6)

The reaction paths envisaged above are analogous to those recently proposed for the exchange reaction (1)[1] and for the destructive bromination of unsymmetrical monosulphides (reactions 7 and 8):[7]




(7) (8)

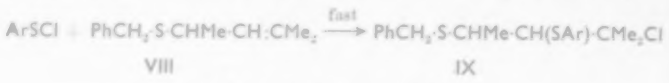
The formation of the intermediate "sulphonium" halides IV and V and their subsequent decomposition by fission of the C–S bonds involving the group R′ which is higher in the cationic stability series conforms to the general pattern of reactivity of sulphides with electrophilic reagents, e.g. their reaction with mercuric chloride and with methyl iodide to give the isolable compounds VI and VII, respectively,

[6] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* pp. 316, 325. Bell, London (1953).
[7] I. L. Knunyants and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1219 (1958).

which undergo decomposition by C–S bond fission involving the group R′ which yields the more stable cation.[8]

VI VII

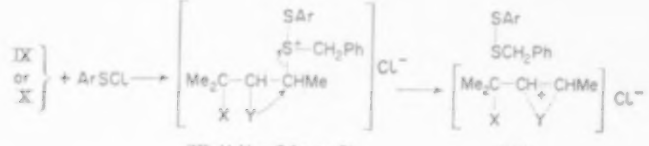
Interaction of the arenesulphenyl chloride (I) with allylically-unsaturated monosulphides involves both addition of I to the double bond and attack on the sulphur atom (as in reactions 2 and 3). For example, benzyl 4-methylpent-3-en-2-yl sulphide (VIII) reacts with ~2 molar equivalents of I to give benzyl 2,4-dinitrophenyl disulphide as one product. Comparison of the data on the above system (see Table) with the kinetics of addition of I to olefins[9] suggests that the reaction involves a fast addition of I to the double bond of VIII to give the adducts IX and/or X (reaction 9), which then undergo a slower reaction with I as indicated below (reaction 10):



VIII IX

and/or $PhCH_2·S·CHMe·CHCl·CMe_2·SAr$

X (9)



XI; X,Y = SAr or Cl XII (10)

$Me_2CX·CHY·CHCl·Me$

or

$Me_2CX·CHCl·CHY·Me$

Two features of this reaction require comment: firstly, that it is the secondary alkyl group in XI, and not the benzyl group, which undergoes displacement by C–S bond fission, contrary to the general pattern observed previously for saturated monosulphides (Table and p. 60); and secondly, that the reaction of I with IX and/or X is much faster than its reaction with other monosulphides containing displaceable secondary alkyl groups. Both features are explicable in terms of participation of the groups ArS- or Cl- vicinal to the C–S bond in XI, giving anchimeric assistance to a preferred cleavage of the designated secondary alkyl C–S bond in XI with the formation of the mesomeric cation in XII.[10]

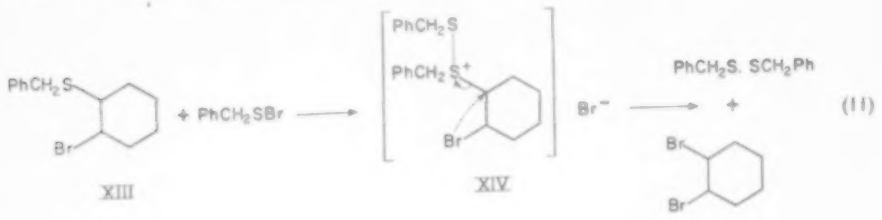
The addition products of I to olefins are substituted monosulphides which in principle should react further with the sulphenyl halide as in reaction (10); that

[8] D. S. Tarbell and D. P. Harnish, *Chem. Rev.* **49**, 1 (1951); J. Goerdeler, in Houben-Weyl, *Methoden der Organischen Chemie* Vol. 9, pp. 175 *et seq.* Georg Thieme, Stuttgart (1955).

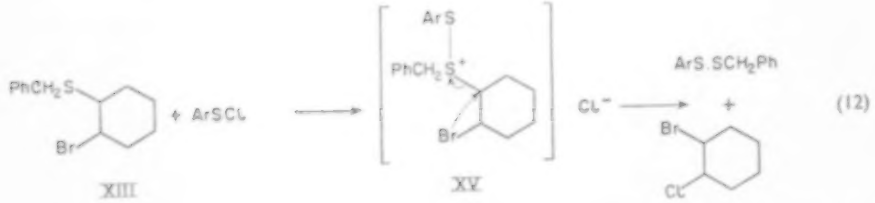
[9] W. L. Orr and N. Kharasch, *J. Amer. Chem. Soc.* **75**, 6030 (1953); **78**, 1201 (1956); D. R. Hogg and N. Kharasch, *Ibid.* **78**, 2728 (1956).

[10] A. Streitwieser, *Chem. Rev.* **56**, 571 (1956).

this is not observed experimentally[3] is now ascribed to the electron-withdrawing 2,4-dinitrophenyl group in the product, $\overleftarrow{ArS}\cdot CR_2\cdot CR_2\cdot Cl$, deactivating the sulphide sulphur towards electrophilic attack by a second sulphenyl chloride molecule. Support for this argument is found in the reactivity of phenylmethanesulphenyl bromide towards cyclohexene. Reaction of equimolar amounts of these compounds in benzene gave the anticipated product XIII. However, reaction of the sulphenyl bromide (2 moles) with the olefin (1 mole) gave a small amount of dibenzyl disulphide as an additional product, whose formation is consistent with reaction (11). Confirmatory evidence for this is the fact that reaction of XIII with I in acetic acid yielded benzyl 2,4-dinitrophenyl disulphide as one product (reaction 12):




XIII XIV (11)




XIII XV (12)

The preferential cleavage of the designated secondary cycloalkyl group in XIV and XV is attributed to anchimeric assistance of the neighbouring bromine atom, leading to the intermediate mesomeric cyclic bromonium ion XVI (cf. p. 61).

XVI

## EXPERIMENTAL

*Materials.* All monosulphides and the unsymmetrical disulphides were analytically pure, being purified commercial samples or materials prepared in these laboratories and described elsewhere. British Drug Houses, "dry acetic acid" (water content, 0·01–0·1%) was used throughout.

*Reaction of* 2,4-*dinitrobenzenesulphenyl chloride* (I) *with monosulphides*

*Analytical procedure* (cf.[4]). To a solution of the sulphide (in amount calculated to allow ca. 25% excess of I) in acetic acid (10 ml) was added a standard solution of I in acetic acid (10·00 ml of 0·1 M) and the mixture allowed to stand at ca. 20° for the desired time. Dry iodate-free sodium iodide (1·5 g) was then added and the mixture shaken for 1·5 min, after which distilled water (100 ml) was added, followed by a measured excess of standard aq sodium thiosulphate. After shaking the mixture for

0·5 min the excess of thiosulphate was determined by titration against standard aq iodine. The extents of reaction (expressed as moles of I reacted per mole of sulphide reactant) as a function of time are detailed in the Table.

*Isolation of disulphide products.* In general, the products from two determinations above were combined, any iodine present was destroyed by aq sodium thiosulphate and the solid material filtered off, washed with water, twice extracted with boiling ethanol, and the combined extracts crystallized. Specific examples of the disulphide products formed are given below.

(1) From the reaction of isopropyl t-butyl sulphide with I was isolated 2,4-dinitrophenyl isopropyl disulphide (63%), m.p. 61·5–62° (Found: C, 39·45; H, 3·75; S, 23·1. Calc. for $C_9H_{10}O_4N_2S_2$: C, 39·4; H, 3·7; S, 23·4%).

(2) From reaction of I with benzyl 4-methylpent-3-en-2-yl sulphide was isolated benzyl 2,4-dinitrophenyl disulphide (59%), m.p. 110·5–111·5, mixed m.p. 110·5–112·5° (Found: C, 48·6, 48·7; H, 3·55, 3·4; S, 19·8. Calc. for $C_{13}H_{10}O_4N_2S_2$: C, 48·4; H, 3·1; S, 19·9 %).

(3) Reaction of dibenzyl sulphide (180 mg, 0·84 mmole) with an acetic acid solution of I (75 ml of 0·01 M) for 48 hr, followed by removal of the solvent *in vacuo* at room temp and two crystallizations of the residue from ethanol yielded benzyl 2,4-dinitrophenyl disulphide (130 mg, 48%), m.p. and mixed m.p. 111–112° (Found: C, 48·6; H, 3·3; S, 19·9%).

(4) Reaction of benzyl 2-methylpent-2-yl sulphide (208 mg, 1 mmole) in acetic acid (10 ml) with a solution of I (100 ml of 0·01 M) for 20 hr and subsequent isolation as in (3) gave benzyl 2,4-dinitrophenyl disulphide (158 mg, 49%), m.p. 111–112°, mixed m.p. 111–112·5° (Found: C, 48·45; H, 3·2; S, 20·0%).

*Reaction of* (I) *with dibenzyl sulphide in benzene*

A mixture of I (235 mg, 1 mmole) and the sulphide (215 mg, 1 mmole) in benzene (9·5 ml) was allowed to react for 14 days at ca. 20°. Removal of the solvent *in vacuo*, extraction of the residue with cold anhydrous ether and crystallization of the insoluble portion from ethanol gave benzyl 2,4-dinitrophenyl disulphide (118 mg, 37%), m.p. 110·5–112° (Found: C, 48·65; H, 3·2; S, 20·2%).

*Reaction of* (I) *with dibenzyl sulphide. Identification of benzyl chloride*

(1) *Control experiment.* A mixture of benzyl chloride (0·652 g, 5 mmoles) and thiourea (0·386 g, 5 mmoles) in ethanol (1·2 ml) was refluxed for 0·5 hr, the solution then cooled and added slowly with stirring to a conc aqueous-ethanolic solution of sodium picrate (1·26 g, 5 mmoles) to give S-benzylisothiuronium picrate (1·584 g, 80%), m.p. 182–183° (from benzene) (Cope *et al.*[11] give m.p. 187–188·5°; however, recrystallization of the above sample from various solvents did not raise the m.p.).

(2) *Examination of reaction products.* A solution of I (1·174 g, 5 mmoles) and the sulphide (1·071 g, 5 mmoles) in acetic acid (15 ml) was caused to react for 283 hr at ca. 20°. Evaporative distillation of the product at $10^{-2}$ mm, addition of the distillate to water and neutralization of the acid with aq sodium hydroxide, followed by extraction with benzene and removal of solvent gave a residue which on treatment with thiourea as in (1) gave S-benzylisothiuronium picrate (1·17 g, 59%), m.p. and mixed m.p. 182–183° (from aq ethanol) (Found: C, 42·2; H, 3·3; S, 8·35. Calc. for $C_{14}H_{13}O_7N_5S$: C, 42·55; H, 3·3; S, 8·1%).

*Reaction of* (I) *with di-isopropyl sulphide*

The reactants (0·01 mole of each) in acetic acid (20 ml) were caused to react at ca. 20° for 529 hr and then at 50° for 209 hr, conditions leading to ca. 97% reaction of I. Separation of volatile material by low-pressure evaporative distillation at room temp left a crystalline residue (2·67 g) which, on extraction with hot ethanol, gave an insoluble residue (78 mg) of bis(2,4-dinitrophenyl) disulphide. Fractional crystallization of the ethanolic extract gave: (i) 2,4-dinitrophenyl isopropyl disulphide (1·97 g), m.p. and mixed m.p. 60·5–61·5° (Found: C, 39·6; H, 3·6; S, 23·7. Calc. for $C_9H_{10}O_4N_2S_2$: C, 39·4; H, 3·7; S, 23·4%); and (ii) a red oil (0·60 g) which partially solidified on standing (Found: C, 39·7; H, 3·55; Cl, 4·55; S, 19·0, 19·3. Calc. for a 64 : 36 wt % mixture of 2,4-dinitrophenyl isopropyl disulphide and 2-chloropropyl 2′,4′-dinitrophenyl sulphide: C, 39·3; H, 3·55; Cl, 4·6; S, 19·1%). The disulphide accounts for 85·7% and the chloromonosulphide for 8·1% of incident I.

[11] A. C. Cope, T. T. Foster and P. H. Towle, *J. Amer. Chem. Soc.* **71**, 3929 (1949).

*Reaction of phenylmethanesulphenyl bromide with cyclohexane*

(1) The sulphenyl bromide, prepared in benzene solution (50 ml) from toluene-$\omega$-thiol (0·02 mole) and N-bromosuccinimide (0·02 mole) by Emde's method,[12] was added (without isolation) to cyclohexene (0·02 mole) in benzene (5 ml) and the mixture allowed to stand for 15 days. Removal of solvent at low pressure gave a pale yellow liquid residue, undistillable at 0·1 mm (bath temp 150°), but which, on short-path distillation at $< 10^{-3}$ mm (bath temp 70–80°), gave a yellow liquid distillate, unstable towards moist air, which consisted mainly of *benzyl 2-bromocyclohexyl sulphide* (XIII) (Found: C, 54·8; H, 5·75; S, 12·8; Br, 23·2. $C_{13}H_{17}SBr$ requires: C, 54·75; H, 6·0; S, 11·25; Br, 28·0%). No dibenzyl disulphide was isolable from the reaction product.

(2) Reaction of the sulphenyl bromide with a 0·5 molar proportion of cyclohexane under the conditions in (1) above gave the adduct XIII and dibenzyl disulphide (50 mg), m.p and mixed m.p. 68·5–70° (Found: C, 68·3; H, 5·85. Calc. for $C_{14}H_{14}S_2$: C, 68·25; H, 5·7%). Confirmation that the dibenzyl disulphide resulted directly from interaction of the adduct XIII with excess sulphenyl bromide was obtained by allowing XIII to react with the sulphenyl chloride I in acetic acid for 14 days at ca. 20° when benzyl 2,4-dinitrophenyl disulphide, m.p. 110–112° (Found: C, 48·4; H, 3·2; S, 20·3%) was obtained.

*Acknowledgements*—We thank Drs. D. Barnard and T. Colclough, and Mr. M. E. Cain for samples of sulphides used in this work which forms part of the programme of research undertaken by the Board of the British Rubber Producers' Research Association.

[12] H. Emde, Ger. Pat. 804572 (1951); *Chem. Abstr.* **46**, 529 (1952).

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# CARBON–CARBON BOND ENERGIES

J. C. EARL
Thurlton, Norwich

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**Abstract**—Although it is difficult to arrive at entirely reliable and precise values for bond energies of the various types of carbon–carbon bonds, it is possible to estimate probable relative values. This is done in the following discussion without involving the heats of sublimation of diamond or graphite, but the requirement still outstanding is an unequivocal value for any one bond of known order.

WE have in diamond a precise standard for the length of the single C–C bond, but data for the energy of the bond are less certain. The heat of sublimation of diamond (124·3 kcal) however precisely it may have been observed experimentally must be interpreted in terms of bond energy with some caution. If it is assumed that it is identical with the heat of dissociation into single carbon atoms, it follows that 62·15 kcal must be the energy of the single C–C bond. There must, however remain some doubt whether dissociation to single carbon atoms is complete and whether other energy-consuming processes are involved.

The heat of sublimation of graphite as a standard in the determination of bond energies is even less satisfactory. Wheland[1] uses the energy equation $a$C (graphite) → $a$C (gas) — 171·7 kcal in replacement of the earlier[2] $a$C (diamond) → $a$C (gas) — 124·3 kcal when calculating the energy of C–C and C–H bonds. In consequence, the value of 58·6 kcal arrived at first for single C–C bonds is replaced by the very different value 83·6 kcal. The element of confusion introduced by this change of presumed fundamental standards makes it difficult to assess the significance of such calculations. It is, therefore, proposed to by-pass them as far as possible, in the following discussion.

When diamond is burnt to carbon dioxide it can be assumed that two processes—breakdown of the molecule to atoms and combustion of atomic carbon—are superimposed. For every carbon set free, two single bonds are broken. The net energy release is the heat of combustion of diamond, which has been determined as 94·505 kcal. Therefore, if $a$ be the energy of the single C–C bond and $c$ the energy involved in the formation of carbon dioxide from atomic carbon and molecular oxygen

$$2a = 94{\cdot}505 + c \qquad (1)$$

No certain value can be assigned to either $a$ or $c$, but the expression is of use for determining the properties of the C–C bonds in the higher paraffins. The heats of combustion of many of the normal paraffins have been determined with accuracy under comparable conditions. For the lower members of the series the increase in heat of combustion with the number of carbon atoms is irregular, but above pentane there is almost complete regularity. For a hydrocarbon $C_nH_{2n+2}$ the processes

[1] G. W. Wheland, *Resonance in Organic Chemistry* p. 115. John Wiley, New York (1955).
[2] G. W. Wheland, *The Theory of Resonance and its Application to Organic Chemistry*. p. 75. John Wiley, New York (1944).

concerned in its combustion to carbon dioxide and water are:

(i) the breaking of $(n - 1)$ C–C bonds $\rightarrow a_1(n - 1)$ kcal
(ii) the breaking of $(2n + 2)$ C–H bonds $\rightarrow b(2n + 2)$ kcal
(iii) the conversion of $n$ atoms of C into carbon dioxide $\rightarrow nc$ kcal
(iv) the conversion of $(2n + 2)$ atoms of H into water $\rightarrow d(2n + 2)$ kcal

Applying this to heptane and nonane we get the two equations:

$$6a_1 + 16b = 1160{\cdot}01 + 7c + 16d \text{ kcal}$$

$$8a_1 + 20b = 1474{\cdot}90 + 9c + 20d \text{ kcal}$$

From these equations $b$ and $d$ can be eliminated giving

$$2a_1 = 99{\cdot}55 + c \qquad (2)$$

From the two expressions (1) and (2) it follows that $a_1$ is greater than $a$ by 2·52 kcal, a piece of information which is of considerable interest and would be more so if a precise value could be assigned to either $a_1$ or $a$.

Pauling's scale of empirical bond energies can be correlated with the order of C–C bonds by means of the equation[3]

$$E = 130{\cdot}9 - 8(4 - N)^2$$

where $E$ is the energy and $N$ the order of the bond. This equation does not, however, fit the case where $N = 0$; one must assume that $E$ would then be zero also, whereas the equation would give it a value of 2·9 kcal. If it is assumed that the general form of the equation is correct, it can be written as $E = x - y(4 - N)^2$. When $N = 0$, $E = 0$ and $x = 16y$. This cuts out one of the constants, leaving $E = y[16 - (4 - N)^2]$. Substituting in this equation various values for $N$, say, 1, 2, 3, 1·55 (graphite), 1·67 (benzene), a series of relative values for $E$ are obtained, namely, $7y$, $12y$, $15y$, $10y$, $10{\cdot}57y$. A precise figure for the energy of any one C–C bond of known order would then enable a self-consistent scale to be established for all C–C bonds. Although this requirement cannot yet be met, interesting results are obtained by assuming that 58·6 kcal, the value judged by Pauling to approximate to the energy of a single bond, is actually the true value. Then $y$ becomes 8·37 and the relative energies given above 58·6, 100·4, 125·5, 83·7 and 88·5 respectively. In this way a means is provided for assigning an energy value to any C–C bond whose length can be measured, since the order and the length are connected by the equation

$$N = \frac{3R_1^2}{R_x^2} - 2$$

($R_1$ being the length of a single C–C bond and $R_x$ the length of the bond being investigated: $3R_1^2$ is numerically 7·155).

A test of the validity of the above arguments is furnished by a calculation based on the energy of the C–C bonds in the higher normal paraffins. As has been shown earlier, this is 2·52 kcal greater than that of the true single bond which we have taken to be 58·6 kcal. By applying the equations given above in reverse, the order (1·050) and the length (1·532 Å) of the paraffin C–C bonds can be calculated. The lengths of the C–C bonds in n-pentane, n-hexane and n-heptane have recently been measured by an electron diffraction method and found to be 1·531, 1·533 and 1·534 Å respectively.[4]

[3] J. C. Earl, *Tetrahedron* **3**, 355 (1958).
[4] R. A. Bonham, L. S. Bartell and D. A. Kohl *J. Amer. Chem. Soc.* **81**, 4765 (1959).

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# KATALYTISCHE OXYDATION VON PRIMÄREN UND SEKUNDÄREN HYDROXYLVERBINDUNGEN MIT SAUERSTOFF AM PLATINKONTAKT IN FLÜSSIGER PHASE

## ÜBER KATALYTISCHE OXYDATIONEN—XIV[1]

K. HEYNS und L. BLAZEJEWICZ
Aus dem Chemischen Staatsinstitut
Institut für Organische Chemie
Universität Hamburg

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**Zusammenfassung**—Unter milden Bedingungen lassen sich in wässriger Lösung oder in organischen Lösungsmitteln mittels Sauerstoff am Platinkontakt primäre Alkohole je nach den Bedingungen zu Aldehyden oder Carbonsäuren, sekundäre Alkohole zu Ketonen oxydieren. Die Oxydation verschiedenster Alkohole wurde systematisch untersucht. Das Verfahren eignet sich besonders zur präparativen Darstellung langkettiger Aldehyde.

Im Jahre 1823 veröffentliche Döbereiner[2] eine Schrift mit dem Titel, *Über neu entdeckte höchst merkwürdige Eigenschaften des Platins* in der er über die *kalte* Umsetzung von Wasserstoff mit Sauerstoff bei Gegenwart von Platin berichtet. 1845 berichtete Döbereiner[3] weiterhin über die Beobachtung, dass Sauerstoff sich bei Gegenwart von Platin und Alkali *viel leichter mit dem Weingeist verbinde*. Verschiedene andere Autoren[4] jener Zeit fanden, dass Mannit-Lösungen, mit Platin verrührt, reduzierende Substanzen lieferten. In diesen wenigen mehr phänomenologischen und präparativ nicht weiter entwickelten Arbeiten ist die Methode der katalytischen Oxydation vor etwa 100 Jahren stecken geblieben und nicht zu einem präparativ verwendbaren Verfahren entwickelt worden.

Wieland[5] hat, an die alten Arbeiten anknüpfend, gezeigt, dass fein verteiltes Platin die Oxydation von Alkoholen in wässriger Lösung katalysiert, Er fand, dass bei dieser Reaktion der Wasserstoff vom Alkohol mittels des Katalysators dehydrierend abgespalten und auf einen geeigneten Acceptor wie Sauerstoff oder Methylenblau übertragen wird und sprach aus diesem Grund die Platinkatalyse als Dehydrase-Modell an. Diese Dehydrierungstheorie hat in den Potentialmessungen von Müller und Schwabe[6] ihre Bestätigung gefunden. Neuerdings wird von Rottenberg und Thürkauf[7] auf Grund von Austauschversuchen mit isotop markiertem $H_2O^{18}$ auch eine gleichzeitige Sauerstoff-Aktivierung diskutiert.

Während auf der einen Seite die Verfahren der katalytischen Hydrierung in vielseitigen speziellen Anwendungsformen immer weiter ausgebaut und vervollkommnet

[1] XIII. Mitt. K. Heyns u. M. Beck, *Chem. Ber.* **91**, 1720 (1958).
[2] J. W. Döebereiner, *Schweigers J. f. Chem. u. Phys.* **38**, 321; **39**, 159 (1823).
[3] J. W. Döebereiner, *Liebigs Ann.* **53**, 145 (1845).
[4] F. von Gorup-Besanez, *Liebigs Ann.* **118**, 259, 273 (1861); F. W. Dafert, *Ber. Dtsch. Chem. Ges.* **17**, 227 (1887); A. Strecker, *Liebigs Ann.* **93**, 370 (1855).
[5] H. Wieland, *Ber. Dtsch. Chem. Ges.* **45**, 484, 2606 (1912); **46**, 3327 (1913); **54**, 2353 (1921).
[6] E. Müller u. H. Schwabe, *Kolloid Z.* **52**, 163 (1930).
[7] M. Rottenberg u. M. Thürkauf, *Helv. Chim. Acta* **42**, 226 (1959).

wurden, hat andererseits die katalytische dehydrierung bzw. Oxydation bis in die jüngste Zeit hinein kaum eine breitere Bearbeitung und Anwendung gefunden. Erst nachdem gezeigt werden konnte, dass durch Oxydation am Platinkontakt selektive Umsetzungen spazieller Art von Polyoxyverbindungen z.B. Kohlenhydrat-Derivaten durchgeführt werden konnten*, erhielt das Verfahren für zahlreiche wichtige organische Substanzgruppen präparative Bedeutung.

Es zeigte sich, dass primäre Alkoholgruppen bevorzugt vor sekundären oxydiert wurden. So wurde L-Sorbose, glatt zu 2-Keto-L-gulonsäure,[8] 1,2-Isopropyliden-D-glucofuranose zur entsprechenden D-Glucuronsäure bei erhöhter Temperatur oxydiert.[9] Zahlreiche Glycoside[10] und am Stickstoff blockierte Aminohexoside[11] sind auf diesem Weg in die Uronide überführt worden, und das Verfahren hat sich als Standardmethode zur Darstellung von Uronsäurederivaten entwickelt.

Bei Cycliten, die OH-Gruppen sowohl in axialer wie in äquatorialer Lage besitzen, werden bei der katalytischen Oxydation selektiv axiale OH-Gruppen oxydiert, z.B. wird aus myo-Inosit myo-Inonose-2 erhalten.[12] Die Anwendung dieses Prinzips hat zur Strukturaufklärung einer Reihe unbekannter neuer Inosite[13] und zu einer Synthese des Streptamins geführt.[14] Ferner sind auch Steroid-Alkohole selektiv oxydiert worden.[15]

Systematische Untersuchungen über die Oxydierbarkeit der verschiedensten Typen von Alkoholen, über die Anwendungsbreite des Verfahrens, sowie über die Auffindung von einheitlichen Reaktionsbedingungen für eine spezielle Anwendung lagen bisher nicht vor und sind Gegenstand der vorliegenden Arbeit.

Mit Hilfe einer Test-Oxydation, in diesem Falle die Oxydationen von Isopropanol zu Aceton, wurde die Einwirkung verschieder Lösungsmittel, die Art und Vorbehandlung des Katalysators, die Giftwirkung von Zusätzen, die pH-Abhängigkeit und Konzentrationsabhängigkeit überprüft. Unter den optimalen Bedingungen wurden dann die einzelnen Typen von Alkoholen oxydiert. Diese Ergebnisse sind in Tabelle 1. zusammengefasst. Die Oxydationen wurden fast ausschliesslich in einer heizbaren Theilacker'schen Hydrierapparatur, die die Bestimmung der Sauerstoffaufnahme gestattetet, durchgeführt. Für die Oxydationen bei Siedetemperatur wurde ein Siedekolben konstruiert, der mit einer geschlossenen Umlaufapparatur verbunden war, bei der der Sauerstoff im Kreislauf umgepumpt wurde.

Als günstigete Lösungsmittel, bei denen die Oxydation am schnellsten verläuft, erwiesen sich entweder stark polare wie Wasser oder unpolare Lösungsmittel wie Benzin, n-Heptan. Ketone wie Aceton und Butanon waren noch gut geeignet. Langsame Oxydation erfolgte in Benzol und Essigester, welcher einen erheblichen Sauerstoffblindwert aufwies. Lösungsmittelgemische waren mit Ausnahme von Aceton–Wasser immer weniger brauchbar.

Zur Oxydation in Wasser wurde ein Platin-Kohle-Katalysator (10%ig) verwendet. Dieser erwies sich als sehr giftempfindlich. Abb. 1. demonstriert die Hemmung der

* Zusammenfass. Übers. vergl. K. Heyns und H. Paulsen, *Angew. Chem.* **69**, 600 (1957).

[8] K. Heyns, *Liebigs Ann.* **558**, 177 (1947).
[9] C. L. Mehltretter, B. H. Alexander, R. L. Mellies u. C. E. Rist, *J. Amer. Chem. Soc.* **73**, 2424 (1951)
[10] C. L. Mehltretter, *Advanc. Carbohydrate Chem.* **8**, 244 (1953).
[11] K. Heyns u. H. Paulsen, *Chem. Ber.* **88**, 188 (1955); K. Heyns u. M. Beck, *Ibid.* **90**, 2443 (1957).
[12] K. Heyns u. H. Paulsen, *Chem. Ber.* **86**, 833 (1953).
[13] L. Anderson, E. S. De Luca, A. Bieder u. G. G. Post, *J. Amer. Chem. Soc.* **79**, 1171 (1957); B. Lindberg u. B. Wickberg, *Arkiv. Kemi* **13**, 447 (1959).
[14] K. Heyns u. H. Paulsen, *Chem. Ber.* **89**, 1152 (1956).
[15] R. P. A. Sneeden u. R. B. Turner, *J. Amer. Chem. Soc.* **77**, 190 (1955).

Oxydation durch Zusatz verschiedener Ionen. Besonders Calcium-Ion hemmt stark die Oxydation, Aluminium-Ion verlangsamt die Reaktion, Borax ist ohne Einfluss. In abgestandenem, destillierten Wasser, welches immer etwas Calcium aus dem Glas herauslöst, dauerte die Oxydation von Isopropanol 700 Minuten. In frisch bidestilliertem Wasser und in hochgereinigten Gefässen war sie bereits in 50 Minuten beendet. Für die Oxydationen in Wasser wurde daher nur frisch bidestilliertes

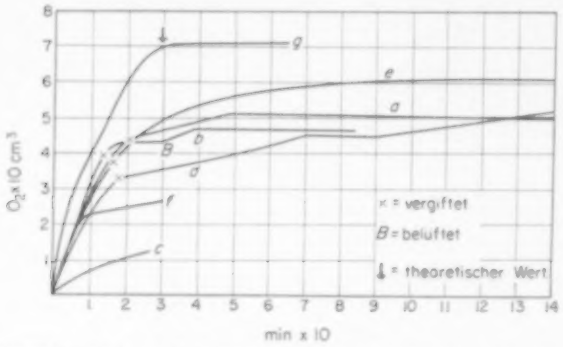


Abb. 1. Die Wirksamkeit von Katalysatorgiften bei der katalytischen Oxydation mit Kohle–Platin–Katalysator.

*a*, Kaliwasserglas; *b*, Calciumchlorid; *c*, Ablauf einer auf Vergiftung mit Calciumchlorid folgenden Dehydrierung; *d*, Aluminiumchlorid; *e*, Borax; *f*, Standard-NaOH; *g*, nicht vergiftete Dehydrierung.

Lösungsmittel verwendet. Mit steigender Kettenlänge der Alkohole fiel die Giftempfindlichkeit ab. Bei der Oxydation des Benzylalkohols und Phenyläthylalkohols konnten sogar schon Lösungen benutzt werden, die aus aufstehendem destillierten Wasser und Alkoholen handelsüblicher Reinheit hergestellt worden waren.

In Wasser liessen sich nur die niederen Glieder primärer Alkohole, Isopropanol und Glykole oxydieren. Dabei mussten die optimalen Oxydationsbedingungen für jede Substanz einzeln ermittelt werden, die Oxydationszeiten lagen zwischen 10–30 Stunden, die Temperaturen zwischen 20°–100°, die Konz. bei 2,5 mMol in 25 ml mit 0,3 g Katalysator.

In neutraler Lösung lieferten primäre Alkohole bei der Oxydation Aldehyde, jedoch tritt durch die teilweise Bildung von Säure Hemmung ein, so dass die Ausbeuten gering sind. Bei Zusatz von 1 Mol. Alkali wird die Säure ständig gebunden, die Lösung bleibt alkalisch und liefert in guten Ausbeuten Carbonsäuren. Bei 2-wertigen Alkoholen z.B. Glykol wird bei Gegenwart von 1 Mol Alkali nur eine Hydroxylgruppe oxydiert und es wird die Oxysäure z.B. Glykolsäure erhalten. Innerhalb der homologen Reihe nimmt die Oxydationszeit mit steigender Kettenlänge stark zu. Auch sind die höheren Glieder nicht mehr wasserlöslich. Es lassen sich aber nur homogene Lösungen oxydieren, da sonst der Katalysator zusammenballt und die Oxydation augenblicklich zum Stillstand kommt. Es gelingt, die höheren Glieder bis zum Octylalkohol durch Zusatz von Dioxan oder hydrotrop mit Na-*p*-toluolsulfat[16] in Lösung zu bringen und zu oxydieren, jedoch ist es empfehlenswerter, die Oxydation dann gleich in organischem Lösungsmitteln vorzunehmen. Die

[16] C. Neuberg, *Biochem. Z.* **76**, 107 (1916).

Oxydation von sekundären Alkoholen zu Ketonen wird durch den pH-Wert der Lösung nicht wesentlich beeinflusst.

In Wasser nicht mehr lösliche Alkohole wurden in organischen Lösungsmitteln oxydiert. Dabei erwies sich ein reiner Platinkatalysator aus Platindioxyd nach Adams-Shriner[17] wirksamer als ein Kohle-Platin-Katalysator. Eine ausgesprochene Wirkung von Katalysatorgiften, wie sie bei Oxydation in wässriger Lösung auftrat, konnte hier nicht beobachtet werden. Das bei der Oxydation gebildete Wasser, welches sich zum Teil an der Katalysatoroberfläche niederschlägt, scheint für den Verlauf der Oxydation eine bedeutsame Rolle zu spielen, denn die Oxydationen gelingt nur in einem bestimmten Konzentrationsbereich. Bei mit Wasser nicht mischbaren Lösungsmitteln (n-Heptan, Benzin) scheidet sich, falls die Konzentration zu gross ist, das Reaktionswasser ab, verklebt den Katalysator und bringt so die Reaktion vorzeitig zum Stillstand. Diese Oxydationen sind daher nur in so verdünnten Lösungen durchzuführen, dass das Reaktionswasser vom Lösungsmittel noch aufgenommen werden kann. In zu verdünnten Lösungen ist die Oxydation bemerkenswerterweise auch nicht möglich. Einen Hinweis, dass eine gewisse Menge Wasser an der Katalysatoroberfläche für die Oxydation vorhanden sein muss, geben auch die Beobachtungen über die Vorbehandlung des Adams-Katalysators. Ein Katalysator, der aus lufttrockenem Platindioxyd (Degussa) hergestellt war, zeigte die schnellsten Oxydationsgeschwindigkeiten, speziell getrocknetes oder in feuchter Luft aufbewahrtes Platindioxyd lieferte wesentlich weniger aktive Kontakte. Bei mit Wasser mischbaren Lösungsmittel (Dioxan, Butanon) wird das bei der Oxydationsreaktion gebildete Wasser aufgenommen und die Lösung bleibt ständig homogen.

Am schnellsten verlaufen die Oxydationen in n-Heptan, bei dem man aber gerade nur in verdünnten Lösungen arbeiten kann. Für grössere Ansätze (in Konz. bis zu 40 proz) bewährten sich bei sekundären Alkoholen Dioxan und Eisessig, bei primären Alkoholen Butanon. Ferner sind Essigester und Benzol geeignet, da diese noch genügend Wasser zu binden vermögen. Die Oxydationszeiten aller dieser Lösungsmittel sind jedoch erheblich länger.

Einwertige primäre Alkohole liefern nach Aufnahme von 1/2 Mol Sauerstoff den Aldehyd. In n-Heptan liegen die Aldehydausbeuten der niederen Glieder zwischen 50–60 proz. Bei längerkettigen Alkoholen steigen sie über 90 proz (Palmitinaldehyd), während die Reaktionszeit stark abnimmt. So lässt sich z.B. Dodecylalkhol in 15 Minuten zu Laurinaldehyd oxydieren. Bei Fortsetzung der Oxydation wird in 2 Stunden quantitativ Laurinsäure erhalten. Das dabei in doppelter Menge entstehende Reaktionswasser beeinflusste die Reaktionszeit nicht wesentlich. Das verfahren bietet somit eine sehr einfache Möglichkeit, langkettige Aldehyde in guten Ausbeuten darzustellen.

Doppelbindungen werden bei der katalytischen Oxydation nicht angegriffen, denn ungesättigte Alkohole lassen sich gleichermassen zu Aldehyden oxydieren, z.B. in 1,5 Stunden Tiglylalkohol zu Tiglinaldehyd in 74 proz Ausbeute. In gleicher Weise reagiert Geraniol. Bei der Oxydation von *cis-trans*-Isomeren bleibt die Konfiguration erhalten, so führt die Oxydation von Olein-bzw. Elaidinalkohol zu den entsprechenden Aldehyden. Karrer und Hess[18] haben bereits die katalytische Oxydation von Vitamin A zu Retinin durchgeführt.

[17] R. Adams u. R. L. Shriner, *J. Amer. Chem. Soc.* **45**, 1071 (1923), **46**, 1683 (1924).
[18] O. Karrer u. W. Hess. *Helv. Chim. Acta* **40**, 265 (1957).

Cyclische sekundäre Alkohole (Cyclohexanol) sind sehr leicht in 1–2 Stunden nahezu quantitativ in die entsprechenden Ketone zu überführen. Nach Sneeden und Turner[15] verhalten sich alkylsubstituierte cyclische Alkohole ähnlich, allerdings nimmt mit zunehmender Ringverzweigung die Ausbeute ab und die Reaktionszeiten zu. Halogenalkohole lassen sich nicht zu den Ketonen oxydieren, sondern werden völlig abgebaut, so wurde bei der Oxydation von α-Chlorcyclohexanol nur Acetaldehyd als Abbauprodukt erhalten. Aromatische sekundäre Alkohole entsprechen in ihrem Verhalten den cyclischen Verbindungen. Auch sie liefern annähernd quantitative Ausbeuten bei allerdings erhöhter Reaktionszeit.

Bei den aliphatischen sekundären Alkoholen wächst die Reaktionszeit mit der Kettenlänge. Sie variiert von 30 Minuten bei Isopropanol bis zu 4 Tagen bei Octanol-2. Alkoholische Gruppen in 2-Stellung sind leichter oxydierbar als in 3-Stellung, also in der Mitte der Kette. Alkohole mit verzweigter Kohlenstoffkette geben schlechtere Ausbeuten, ferner scheint die Oxydation zu $C_6$-Ketonen besonders erschwert zu sein. Einzelheiten der Oxydation der verschiedenen Alkohole sind aus der Tabelle 1 ersichtlich. Im experimentellen Teil sind einige Beispiele aufgeführt. Die nicht gesondert genannten Oxydationen entsprechen in den Reaktionsbedingungen denen der in der Tabelle 1 gekennzeichneten Beispiele.

## EXPERIMENTELLER TEIL

1. *Herstellung des Katalysators*

(a). *Platin-Kohle-Katalysator*[8]: 76,2 g Carboraffin wurden mit halbkonzentrierter Salzsäure dreimal ausgekocht, abgesaugt und chlorfrei gewaschen. Die gereinigte Kohle wurde in 1,5 l Wasser suspendiert, 7,5 g Platin als $H_2PtCl_6$ in 80 cc Wasser gelöst und 15 cc konzentrierter Salzsäure zugefügt. Dann wurde bei Zimmertemperatur hydriert. Die Wasserstoffaufnahme betrug in 8½ Stn 3,6 l. Der Katalysator wurde abgesaugt, chlorfrei gewaschen und getrocknet. Ausb. 74 g.

(b). *Herstellung von Platindioxyd:* Erfolgte nach Adams[17] aus $(NH_4)_2PtCl_6$ in einer Platinschale. Ein in einer Porzellanschale statt einer Platinschale erschmolzener Katalysator war häufig inaktiver. Die besten Ergebnisse wurden mit einem Platindioxyd-Katalysator der Firma Degussa erzielt, der in gleichbleibender Aktivität geliefert wird.

(c). *Lösungsmittel:* Es wurden reinste Handelspräparate verwendet. n-Heptan wurde über Natrium getrocknet und destilliert. Eisessig wurde mit $KMnO_4$ in üblicher Weise stabilisiert. Dioxan, puriss, "Merck" enthält Acetaldehyd, Spuren Glycolacetal und Peroxyd und war als Lösungsmittel für Oxydationen nur dann geeignet, wenn es über eine $Al_2O_3$-Säule (Woelm, basich) gereinigt und fraktioniert destilliert wurde. Als Lösungmittels angewendetes Dioxan wurde stets auf diese Art gereinigt.

2. *Oxydationen von primären Alkoholen*

(a). *Modelloxydationen von n-Butanol in Wasser und n-Heptan* 0,19 g n-Butanol, 25 cc Wasser, 5,0 cc N-NaOH, 0,25 cc Dioxan und 0,3 g Platin-Kohle-Katalysator wurden in eine Schüttelente gebracht, die auf die Oxydationstemperatur von 80° angeheizt war. Das Substrat wurde mit Luft geschüttelt und der verbrauchte Saurestoff manometrisch bestimmt. Nach 17 Std waren 85 cc Sauerstoff aufgenommen. Nach Abfiltrieren des Katalysators wurden die Natrium-Ionen mit Lewatit C ($H^+$-Form) entfernt und im Durchlauf 0,23 g n-Buttersäure durch Titration gefunden. Ausb. theoretisch. Buttersäurephenylphenacylester F. 82°.

Die Oxydation von n-Butanol in n-Heptan zu n-Butyraldehyd wurde wie Vers. 2b ausgeführt. Es wurden 0,27 g n-Butanol in 15 cc n-Heptan mit 0,18 g zunächst vorhydriertem Platindioxyd bei 40° mit Luft statt Sauerstoff oxydiert. Fn 5 Std wurden 44 cc (96% d.Th.) Sauerstoff aufgenommen. 0,55 g n-Butyraldehyd-2,4-dinitrophenylhydrazon F. 103–107° (57% d. Th.), umkrist aus Petroläther F. 121°. Die Titration ergab, dass 10% des Alkohols zu Buttersäure weiteroxydiert worden war.

TABELLE 1

| Substrat | Lösungsmittel | Katalysator | Oxydationszeit in Stdn. | Oxydationstemperatur in C° | Oxydationsprodukt | Ausbeute in % | Beding. Nr. im experiment. T. | Bemerkungen |
|---|---|---|---|---|---|---|---|---|
| *Primäre Alkohole* | | | | | | | | |
| (a) *Aliphatische, gesättigte, einwertige Alkohole* | | | | | | | | |
| Äthanol | Wasser | Pt–C | ½ | 20 | Essigsäure | 100 | 2a | alkalisch |
| n-Propanol | Wasser | Pt–C | 11 | 66 | Propionsäure | 98 | 2a | alkalisch |
| n-Butanol | n-Heptan | $PtO_2$ | 5 | 41 | Butyraldehyd | 57 | 2a | |
| | Eisessig | $PtO_2$ | 46 | 15 | desgl. | 33 | 2a | |
| | Wasser | Pt–C | 17 | 80 | Buttersäure | 100 | 2a | alkalisch Dioxan |
| n-Pentanol | n-Heptan | Pt–C | 5 | 60 | Valeraldehyd | 51 | 2b | |
| | Dioxan | $PtO_2$ | 12 | 17 | desgl. | 29 | 2a | 79% $O_2$ Ums |
| | Eisessig | $PtO_2$ | 13 | 19 | desgl. | 39 | 2a | |
| | Pivalinsäure | $PtO_2$ | 68 | 61 | desgl. | 33 | 2a | sehr unrein |
| n-Hexanol | Wasser | Pt–C | 25 | 93 Siedetemperatur | Capronsäure | 99 | 2k | alkalisch Dioxan |
| n-Heptanol | n-Heptan | $PtO_2$ | 1 | 60 | Önanthaldehyd | 26 | 2b | 135% $O_2$ Ums |
| Dodecylalkohol | n-Heptan | $PtO_2$ | ½ | 60 | Laurinaldehyd | 77 | 2b | |
| | Methyläthylketon | $PtO_2$ | 42 | 40 | desgl. | 78 | 2c | präparativ |
| | n-Heptan | $PtO_2$ | 2 | 60 | Laurinsäure | 96 | 2d | |
| Myristinalkohol | n-Heptan | $PtO_2$ | ½ | 60 | Myristinaldehyd | 91 | 2h | |
| Cetylalkohol | n-Heptan | $PtO_2$ | 7 | 59 | Palmitinaldehyd | 95 | 2i | |
| Stearylalkohol | n-Heptan | $PtO_2$ | ½ | 60 | Stearylaldehyd | 77 | 2k | |
| (b) *Aliphatische, gesättigte mehrwertige Alkohole* | | | | | | | | |
| Glykol | Wasser | Pt–C | 11 | Siedetemp. | Oxalsäure | 51 | 2m | alkalisch |
| | Wasser | Pt–C | 6 | desgl. | Glykolsäure | 100 | 2l | 1 Mol Alkali |
| Butandiol-1,4 | Wasser | Pt–C | 32 | desgl. | Bernsteinsäure | 55 | 2m | alkalisch |
| Dekandiol-1,10 | n-Heptan | $PtO_2$ | 1,5 | 60 | Sebacindialdehyd | 54 | 2n | |
| (c) *Aliphatische, ungesättigte, einwertige Alkohole* | | | | | | | | |
| Tiglylalkohol | n-Heptan | $PtO_2$ | 2 | 60 | Tiglinaldehyd | 77 | 2e | |
| Geraniol | n-Heptan | $PtO_2$ | 1,5 | 60 | Citral | 63 | 2e | |
| Oleinalkohol | n-Heptan | $PtO_2$ | 3 | 60 | Oleinaldehyd | 47 Rohprod. | 2f | 14% reiner Aldehyd |
| Elaidinalkohol | n-Heptan | $PtO_2$ | 3 | 60 | Elaidinaldehyd | 73 Rohp. | 2f | 22% reiner Aldehyd |

TABELLE 1 (*contd*)

| Substrat | Lösungsmittel | Katalysator | Oxydationszeit in Stdn. | Oxydationstemperatur in C° | Oxydationsprodukt | Ausbeute in % | Beding. Nr. im experiment. T. | Bemerkungen |
|---|---|---|---|---|---|---|---|---|
| (d) *Aromatische Alkohole* | | | | | | | | |
| Benzylalkohol | n-Heptan | $PtO_2$ | 1 | 60 | Benzaldehyd | 78 | 2g | |
| | Wasser | Pt–C | 10 | Siedetemp. | Benzoesäure | 97 | 2g | alkalisch + Toluolsulfosäure |
| Phenyläthylalkohol | n-Heptan | $PtO_2$ | 1,5 | 60 | Phenylacetaldehyd | 34 | 2b | |
| | Wasser | PtC | 12 | Siedetemp. | Phenylessigsäure | 90 | 2g | alkalisch + Toluolsulfosäure |
| *Sekundäre Alkohole* | | | | | | | | |
| (a) *Aliphatische Alkohole* | | | | | | | | |
| Isopropanol | n-Heptan | $PtO_2$ | ½ | 17 | Aceton | 91 | 3a | |
| | Wasser | Pt–C | 1 | 60 | desgl. | 85 | 2a | ohne Alkali |
| | Dioxan | $PtO_2$ | 23 | 17 | Aceton | 63 | 3a | |
| | Essigester | Pt–C | 342 | 18 | desgl. | 76 | 3a | präparativ |
| n-Pentanol-2 | n-Heptan | $PtO_2$ | 1 | 17 | Pentanon-2 | 77 | 3a | |
| | Normal-Benzin | $PtO_2$ | 8,5 | 20 | desgl. | 62 | 3a | |
| | Dioxan | $PtO_2$ | 24 | 18 | desgl. | 54 | 3a | |
| Pentanol-3 | n-Heptan | $PtO_2$ | 5,5 | 16 | Pentanon-3 | 71 | 3a | |
| | Eisessig | $PtO_2$ | 120 | 32 | desgl. | 70 | 3a | |
| n-Hexanol-2 | n-Heptan | $PtO_2$ | 6 | 17 | Hexanon-2 | 56 | 3a | |
| | Dioxan | $PtO_2$ | 24 | 20 | desgl. | 75 | 3a | |
| Methylisobutylcarbinol | Dioxan | $PtO_2$ | 26 | 20 | Methylisobutylketon | 56 | 3a | |
| Octanol-2 | n-Heptan | $PtO_2$ | 96 | 20 | Octanon-2 | 80 | 3a | |
| (b) *Alicyclische und aromatische Alkohole* | | | | | | | | |
| Cyclopentanol | n-Heptan | $PtO_2$ | ¾ | 20 | Cyclopentanon | 82 | 3b | |
| Cyclohexanol | n-Heptan | $PtO_2$ | 1,5 | 20 | Cyclohexanon | 92 | 3b | |
| | Normal-Benzin | $PtO_2$ | 4 | 18 | desgl. | 90 | 3b | |
| | Normal-Benzin | Pt–C | 24 | 48 | desgl. | 60 | 3b | |
| | Essigester | $PtO_2$ | 8 | 20 | desgl. | 59 | 3b | |
| α-Chlorcyclohexanol | Dioxan | $PtO_2$ | — | 18 | Acetaldehyd | — | 3b | wird abgebaut |
| Cycloheptanol | n-Heptan | $PtO_2$ | 1 | 17 | Cycloheptanon | 99 | 3b | |
| Benzhydrol | n-Heptan | $PtO_2$ | 23 | 37 | Benzophenon | 98 | 3c | |
| 2-Methylcyclohexanol | Essigester | $PtO_2$ | 18 | 20 | 2-Methylcyclohexanon | 50 | Lit. 15 | |

(b). *Oxydation von Dodecylalkohol zu Laurinaldehyd in n-Heptan* 0,64 g Dodecylalkohol in 20 cc n-Heptan wurden mit 0,18 g Platindioxyd in die Schüttelente einer Theilacker'schen Hydrierapparatur gebracht. Die Luft wurde durch dreimaliges Evakuieren gegen Wasserstoff ersetzt und der Katalysator unter Schütteln vorhydriert. 40 cc Wasserstoff wurden aufgenommen. Der Wasserstoff wurde durch dreimaliges Evakuieren durch Sauerstoff ersetzt, die Schüttelente auf die Oxydationstemperatur von 60° gebracht und nunmehr mit Sauerstoff geschüttelt. Nach 15 min. waren 42 cc Sauerstoff (104% d Th.) aufgenommen. 1,25 g Rohhydrazon F. 92°, ergaben nach Umkristallisation 0,97 g bei 105° schmelzendes Laurinaldehyd-2,4-dinitrophenyl-hydrazon (76% d. Th.).

(c). *Oxydation von Dodecylalkohol zu Laurinaldehyd in Methyläthylketon:* 2,87 g Dodecylalkohol in 30 cc Methyläthylketon wurden mit 0,19 g Platindioxyd in die Schüttelente gegeben und der Katalysator bei Zimmertemperatur vorhydriert. Nach Aufnahme von 52 cc Wasserstoff wurde der Wasserstoff durch Sauerstoff ersetzt, die Schüttelente auf 40° angeheizt und mit Sauerstoff geschüttelt. Nach 42 Std waren 188 cc Sauerstoff (103% d. Th.) aufgenommen. Nach vollständiger Abtrennung des Butanons wurde in Isopropanol aufgenommen und das 2,4-Dinitrophenylhydrazon gefällt. 4,4 g Laurinaldehyd-2,4-dinitrophenylhydrazon, F. 93–101° (78% d. Th.).

(d). *Oxydation von Dodecylalkohol zu Laurinsäure in n-Heptan* 0,67 g Dodecylalkohol in 25 cc n-Heptan wurden mit 0,19 g Platindioxyd bei 60° wie bei Versuch 2 b oxydiert. Die Oxydation kam nach Aufnahme von 82 cc Sauerstoff (98% d. Th.) nach 2 Std zum Stillstand. Die Lösung wurde vom Katalysator befreit, mit Natronlauge ausgezogen und nach Ansäuern die Laurinsäure ausgeäthert. Ausb. 0,74 g (87% d.Th.) F. 40–47°. Papierchromatisch mit Laurinsäure identisch[18] ($R_f$-Wert 0,49).

(e). *Tiglinaldehyd aus Tiglylalkohol:* 0,19 g Platindioxyd wurden in 15 cc n-Heptan bei Zimmertemp. vorhydriert. Der Wasserstoff wurde durch reinen Sauerstoff ausgetauscht, die Ente auf die Oxydationstemperatur 60° gebracht, 0,32 g Tiglylalkohol in 15 cc n-Heptan eingefüllt und mit Sauerstoff geschüttelt. Die Oxydation wurde nach Aufnahme der theoretisch zu erwartenden Menge Sauerstoff (44 cc) nach 2 Std abgebrochen. Es wurden 0,75 g Tiglinaldehyd-2,4-dinitrophenylhydrazon F. 214° (77% d. Th.) erhalten. Umkristallisieren aus Chloroform. F. 215–216°.

$C_{11}H_{12}N_4O_4$(264,2) Ber. C 50,01 H 4,54 N 21,05
Gef. C 50,00 H 4,58 N 21,21

(f). *Oxydation des Oleylalkohols in n-Heptan:* Während handelsüblicher Oleylalkohol unter den angewendeten Bedingungen nicht oxydierbar war, konnten seine durch chromatographische Reinigung an $Al_2O_3$ (Woelm, neutral) gewonnenen isomeren Bestandteile Oleinalkohol und Elaidinalkohol oxydiert werden.

(1) Oleinaldehyd aus Oleinalkohol: 0,20 g Platindioxyd in 15 cc n-Heptan wurden wie bei Versuch 2 (e) vorhydriert, anschliessend 0,83 g Oleinalkohol in 15 cc n-Heptan zugegeben und wie bei 2(e) bei 60° oxydiert. Nach Aufnahme von 40,5 cc Sauerstoff in 3 Std (110% d. Th.) wurde abgebrochen. 0,64 g Oleinaldehyd-2,4-dinitrophenylhydrazon (47% d. Th.) welches nach einmaligen Umkristallisieren aus Methanol bei 68–69° schmolz.

$C_{24}H_{32}N_4O_4$(446,6) Ber. C 64,54 H 8,58 N 12,55%
Gef. C 64,24 N 8,48 N 12,71%

(2) Elaidinaldehyd aus Elaidinalkohol: Wie bei Oleinalkohol 0,83 g mit 0,20 g Platindioxyd in 15 cc n-Heptan bei 60° oxydieren. Nach 3 Std betrug die Sauerstoffaufnahme 35 cc (theoretischer Wert). 0,96 g Rohhydrazon (73% d. Th.). Umkristallisieren aus Petroläther und Methanol ergab ein bei 104–105° schmelzendes 2,4-Dinitrophenylhydrazon.

$C_{24}H_{32}N_4O_4$(446,6) Ber. C 64,54 H 8,58 N 12,55%
Gef. C 63,97 H 8,76 N 13,13%

(g). *Modell-Oxydation von Benzylalkohol in Wasser und Heptan:* 0,31 g Benzylalkohol, 25 cc Wasser, 7 cc 0,1N-Na-Toluolsulfonat, 8,4 cc N-NaOH und 0,3 g Platin-Kohle-Katalysator wurden unter Lufteinleiten am Rückfluss erhitzt, bis die Lösung nach, 10 Std homogen war. Nach dem Ansäuern wurde Benzoesäure in 97% d. Th. Ausbeute isoliert.

0,42 g Benzylalkohol in 25 cc n-Heptan wurden mit 0,18 g Platindioxyd wie 2 b bei 60° oxydiert.

[18] H. P. Kaufmann u. W. H. Nitsch, *Fette Seifen Austreichunittel* **56**, 154 (1954).

Nach 1¼ Std wirden 47 cc Sauerstoff aufgenommen. Es wurden 78% d. Th. Benzaldehyd-2,4-Dinitrophenylhydrazon erhalten.

(h). *Myristinaldehyd aus Myristinalkohol:* 0,78 g Myristinalkohol in 25 cc n-Heptan wurden mit 0,17 g Platindioxyd bei 60° wie 2(b) oxydiert. Fn 25 Min wurden 44 cc Sauerstoff (105% d. Th.) aufgenommen. 1,3 g Rohhydrazon ergab nach Umkristallisieren aus Benzin Myristinaldehyd-2,4-dinitrophenylhydrazon in 91% Ausb.

(i). *Palmitinaldehyd aus Cetylalkohol:* 0,78 g Cetylalkohol wurde wie 2(b) oxydiert. Nach 7½ Std war die theoretische Menge Sauerstoff (37 cc) aufgenommen. 1,28 g Palmitinaldehyd-2,4-dinitrophenylhydrazon, F. 95° (95% d. Th.).

(k). *Stearylaldehyd aus Stearylalkohol:* 0,87 g Stearylalkohol wurde wie 2(b) oxydiert. Nach 30 Min. 40 cc Sauerstoffaufnahme. 1,32 g Stearylaldehyddinitrophenylhydrazon, F. 107–108° (92% d. Th.).

(l). *Modell-Oxydation von Äthylenglykol zu Glykolsäure in Wasser:* 0,34 g Glykol in 25 cc Wasser, 9,5 cc N-NaOH mit 0,3 g Platin-Kohle-Katalysator wurden bei Siedetemperatur mit Luft in einer Umlaufapparatur oxydiert. Nach 6 Std waren 140 cc Sauerstoff aufgenommen. Die Aufarbeitung der oxydierten Lösung ergab, durch Titration, 0,43 g Glykolsäure. Oxalsäure war nicht nachweisbar. Das Papierchromatogramm zeigte nur Glykolsäure. $R_f$-Wert 0,47.[19] Die Ausbeute ist theoretisch.

(m). *Modelloxydation von Äthylenglykol zu Oxalsäure in Wasser*: 0,21 g Glykol in 25 cc Wasser, 7,1 cc N-NaOH und 0,3 g Platin-Kohle-Katalysator wurden bei Siedetemperatur mit Luft oxydiert. Nach 11 Std waren 187 cc Sauerstoff aufgenommen. 51% Oxalsäure als Ca-Oxalat. Verbindungen mit Carbonylfunktionen waren in der Oxydationslösung nicht nachweisbar.

(n). *Sebacindialdehyd aus Decandiol*-1,10: 0,7 g Decandiol wurde in 25 ml Heptan wie Versuch 2(b) bei 60° oxydiert. Nach 1,5 Std waren 1 Mol Sauerstoff aufgenommen. Es ergab sich in 54% Ausb. ein Hydrazon F. 147°, das identisch mit dem von Weygand und Mitarbeitern[21] beschriebenen Sebacindialdehyd-2,4-dinitrophenylhydrazon ist.

3. *Oxydation von sekundären Alkoholen*

(a). *Octanon* 2 *aus n-Octanol*-2: 0,46 g Octanol-(2) in 15 cc n-Heptan wurden wie Versuch 2(b) mit 0,19 g Platindioxyd bei 20° mit Sauerstoff oxydiert. Nach 4 Tagen waren 37 cc Sauerstoff (87% d. Th.) aufgenommen. 0,95 g Rohhydrazon. Nach Reinigung an Bentonit-Kieselgur[20] wurden 0,61 g Octanon-(2)-2,4-dinitrophenylhydrazon (80% d. Th.) erhalten. Umkristallisiert aus Petroläther F. 69°.

(b). *Oxydation von Cyclopentanol:* 0,40 g Cyclopentanol in 10 cc n-Heptan und 0,20 g Platindioxyd wurden bei 20° mit Sauerstoff wie Versuch 2(b) oxydiert. Nach 40 Min. waren 47 cc Sauerstoff (82% d. Th.) aufgenommen. 1,0 g Cyclopentanon-2,4-dinitrophenylhydrazon, F. 143°. Umkristallisieren aus Alkohol–Essigester F. 144–145°. Ausb. 82% d. Th.

(c). *Oxydation von Benzhydrol:* 0,76 g Benzhydrol in 75 cc n-Heptan wurden bei 37° mit 0,19 g Plantindioxyd und Sauerstoff wie Vers. 2(b) oxydiert. Nach 23 Std waren 48 cc Sauerstoff aufgenommen (99% d. Th.) Nach Abdampfen des Lösungsmittels 0,145 g Benzophenon (98% d. Th.). Benzophenonoxim F. 144,5°.

[20] J. A. Elvridge u. M. Whalley, *Chem. & Ind.* 589 (1955).
[21] F. Weygand, G. Eberhardt, H. Linden, F. Schäfer u. F. Eigen, *Angew. Chem.* 65, 525 (1953).

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# CARCINOGENESIS BY THIOPHENE ISOSTERS OF POLYCYCLIC HYDROCARBONS

## SYNTHESIS OF CONDENSED THIOPHENES

B. D. TILAK
Department of Chemical Technology, University of Bombay

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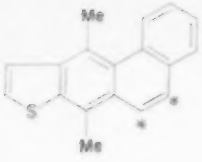
**Abstract**—Contributions by the author extending over the last 15 years on two related topics have been reviewed: (1) Carcinogenesis by thiophene isosters of polycyclic hydrocarbons in connexion with the study of the rôle of the 9,10-double bond in phenanthrene (K region) and (2) Synthesis of condensed thiophenes and thiapyrans. The survey also includes a considerable amount of unpublished work.

### *Thiophene isosters of polycyclic carcinogenic hydrocarbons*

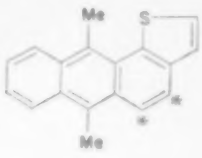
CHEMICAL carcinogenesis has been extensively investigated and several reviews on the subject are available.[1] Among the large number of chemical carcinogens, the polycyclic hydrocarbons are the most systematically studied in view of their structural relationship to the naturally occurring compounds such as, the steroids on the one hand, and their association with certain forms of occupational cancer on the other. Series of closely related hydrocarbons have been prepared with the view to study the relationship between chemical structure and biological activity. Majority of polycyclic hydrocarbons, that have proved carcinogenic, are phenanthrene derivatives suitably substituted by alkyl groups or with fused aryl ring attached to phenanthrene. Many heterocyclic analogues of these carcinogenic hydrocarbons such as, acridine, carbazoles and thiophene derivatives have also proved to be carcinogenic.[1] These facts led Robinson to suggest that the essential structural feature for carcinogenicity in the polycyclic hydrocarbons may be an activated phenanthrene bridge (the 9,10-double bond in phenanthrene shown by asterisks in formulae) which needs to be unsubstituted.[2] With this end in view, Robinson and Tilak initiated a programme of synthesis of thiophene isosters of carcinogenic hydrocarbons, wherein the sulphur atom in the thiophene ring replaced the key phenanthrene bridge.[3]

In this connexion, compounds III, IV and IVA were prepared.[3,4] As against the activity of I and II, prepared earlier[5,6] III was only slightly active when painted on mice and inactive when injected subcutaneously.[1b] The inactivity of III was

[1] (*a*) A. Haddow, *Brit. Med. Bull.* **4**, 314, 331 (1947).
(*b*) J. L. Hartwell, *Survey of Compounds Tested for Carcinogenic Activity*. U.S. Public Health Service (1951).
(*c*) G. M. Badger, *Roy. Aust. Chem. Inst. J. & Proc.* **17**, 14 (1950).
(*d*) Ng. Ph. Buu-Hoi, *Chem. Progr.* **13**, 23 (1952).
(*e*) G. M. Badger, *Advances in Cancer Research* Vol. II, pp. 73–127. Academic Press, New York (1954).
[2] R. Robinson, *Brit. Med. J.* **1**, 945 (1946).
[3] B. D. Tilak, D. Phil. Thesis Oxford University (1946).
[4] B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 131 (1951).
[5] R. B. Sandin and L. F. Fieser, *J. Amer. Chem. Soc.* **62**, 3102 (1940).
[6] E. B. Hershberg and L. F. Fieser, *J. Amer. Chem. Soc.* **63**, 2563 (1941).




I

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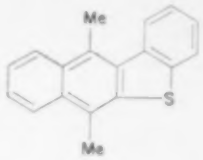
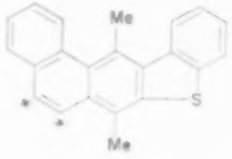
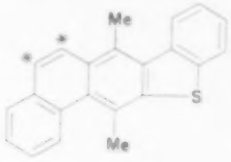



III

attributed to the absence of the phenanthrene bridge, since high activity again emerged in the case of IV and IVA which contain a phenanthrene bridge.




IV




IV a

While the above data was being collected, Pullman *et al.* and Coulson approached the problem from quantum mechanical considerations. Summaries of their conclusions are available in recent literature.[7,8] Since the first step in carcinogenesis involves a reaction of the carcinogen and a cellular receiver probably of an electrophilic nature, Pullmann[7] postulated that the "K-region" should be sufficiently active and that the "L-region" (meso positions in anthracene residue) should be inactive (by substitution, e.g. by methyl groups). The activities of these centres were expressed in terms of electrical indices calculated by Pullmann on the basis of bond localization energies. There are, however, certain exceptions which are difficult to explain on the basis of the Pullmann hypothesis.

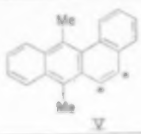
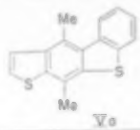
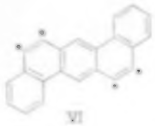
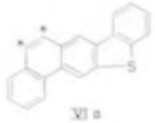
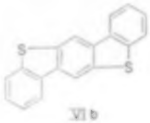
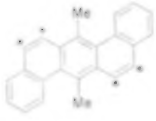
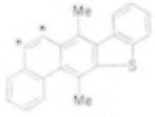
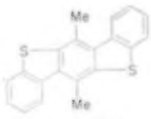
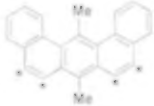
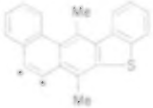
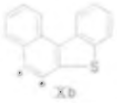
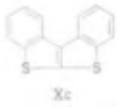
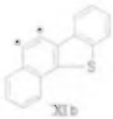
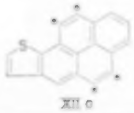
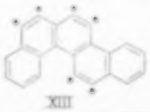
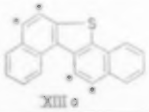
The interaction at the phenanthrene bridge in the metabolism of 1:2,5:6-dibenzanthracene has been demonstrated by Heidelberger.[9] This work indicates that the phenanthrene bridge is involved in carcinogenesis by 1:2,5:6-dibenzanthracene.

The synthesis of key thiosters of carcinogenic hydrocarbons wherein the "K-region" is replaced by isosteric substitution by means of thiophene has been continued by the author.[4] Thus thiosters of the following carcinogens were prepared: 9,10-dimethyl-1:2-benzanthracene (V), 1:2,5:6-dibenzanthracene (VI), 9,10-dimethyl-1:2,5:6-dibenzanthracene (VII), 1:2,7:8-dibenzanthracene (VIII), 9,10-dimethyl-1:2,7:8-dibenzanthracene (IX), 3:4-benzphenanthrene (X), chrysene (XI), 3:4-benzpyrene (XII) and 1:2,5:6-dibenzphenanthrene (XIII). The phenanthrene-bridges referred to hereafter as PB/s are shown by asterisks and the thiosters synthesized are shown alongside with the hydrocarbons in Chart I.

*Thiosters of* 9,10-*dimethyl*-1:1-*benzanthracene* (V). The carcinogenic activity of the thiosters I, II and III has been discussed earlier. Isoster VA has also been prepared,[10] but could not be tested for want of material.

[7] A. Pullmann and B. Pullmann, *Advances in Cancer Research* Vol. III, p. 1711, Academic Press, New York (1955).
[8] C. A. Coulson, *Advances in Cancer Research* Vol. I, pp. 1–56, Academic Press, New York (1953).
[9] P. M. Bhargava, H. I. Halder and C. Heidelberger, *J. Amer. Chem. Soc.* **77**, 2877 (1955); **78**, 3671 (1956).
[10] V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res., India* **14B**, 11 (1955).

Chart 1

| Carcinogenic hydrocarbons | Thiosters |
|---|---|
|  V | I II III  V a |
|  VI |  VI a  VI b |
|  VII |  IV a  VII b |
| VIII | VIII a  VIII b |
|  IX |  IV IX b |
| X | X a  X b  X c |
| XI | XI a  XI b  XI c |
| XII |  XII a |
|  XIII |  XIII a |

*Thiosters of* 1:2,5:6-*dibenzanthracene* (VI). In compound VIB both the PBs are replaced by sulphur[11] and the compound has proved inactive.[12] Compound VIA, wherein only one of the two PBs in VI is replaced, has been synthesized very recently, and remains to be tested.[13]

*Thiosters of* 9,10-*dimethyl*-1:2,5:6-*dibenzanthracene* (VII). The two PBs in VII have been replaced stepwise as in IVA[3,4] and VIIB.[10] Compound IVA is a much more powerful carcinogen than VII[1b] and the high activity was attributed to a single activated PB instead of two competitive PBs as in VII.[4] The key thioster VIIB, wherein both the PBs are removed, however, proved highly active contrary to the expectation that it would be inactive.[12]

*Thioster of* 1:2,7:8-*dibenzanthracene* (VIII). Thiosters VIIIA[13] and VIIIB[14] have been recently synthesized wherein the two PBs in VIII have been removed stepwise. These compounds have yet to be tested.

*Thiosters of* 9,10-*dimethyl*-1:2,7:8-*dibenzanthracene* (IX). When one of the two PBs in IX was replaced, a highly active carcinogen IV resulted as expected.[4] However, the key thioster IXB, wherein both the PBs were removed[15], also proved to be highly carcinogenic, contrary to its expected inactivity.[12]

*Thiosters of* 3:4-*benzphenanthrene* (X). All the three thiosters XA,[15] XB,[16,17] and XC[18] of this weakly active carcinogen X have proved inactive.[1b,12]

*Thiosters of chrysene* (XI). Conflicting reports have appeared as regards the carcinogenic activity of chrysene.[1b] Out of the three thiosters XIA,[20] XIB[16] and XIC,[19] the key compound XIC, wherein both the PBs are removed, has proved noncarcinogenic.[12] Compounds XIA and XIB are also inactive.[1b,12]

*Thiosters of* 3:4-*benzpyrene* (XII). This thioster XIIA[21] in which the two K-regions of 3:4-benzpyrene XII are unaffected is under study for its carcinogenic activity.

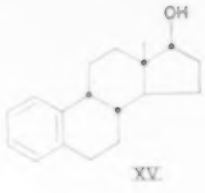
*Thiosters of* 1:2,5:6-*dibenzphenanthrene* (XIII). As against the weak carcinogenic activity of XIII[1b] its thioster 1:2,5:6-dibenzo-9-thiafluorene (XIIIA)[17] has given a highly toxic initial reaction when given subcutaneously to mice.[12a] The test is still in progress.

*Thiosters of phenolic steroids*. Compounds XIVA[22] and XVA[23] which are thiosters of 3-desoxyequilenin (XIV) and 3-desoxyisoestradiol (XV), were synthesized as a preliminary step in the synthesis of B-nor-6-thiaequilenin (XIVB) and B-nor-6-thiaestradiol (XVB). It is of interest to compare the carcinogenic and estrogenic properties of these thiosters and the corresponding natural steroids.

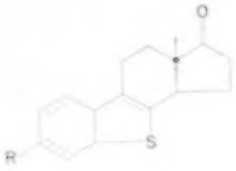
In conclusion it may be said that the interrelation between carcinogenicity and the structure of polycyclic hydrocarbons and their thiosters does not appear to be simple.

[11] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **17B**, 260 (1958).
[12] K. J. Ranadive and S. S. Waravdekar, *J. Nat. Cancer Inst.* **18**, 555 (1957).
[12a] K. J. Ranadive and S. S. Waravdekar, Private communication.
[13] G. N. Pillai and B. D. Tilak, Unpublished work.
[14] L. J. Pandya, G. N. Pillai and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 198 (1959).
[15] V. V. Ghaisas, K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 114 (1953).
[16] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 564 (1953).
[17] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **38A**, 271 (1953).
[18] R. B. Mitra, L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 348 (1957).
[19] V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 345 (1957).
[20] B. D. Tilak, *Proc. Indian. Acad. Sci.* **33A**, 71 (1951).
[21] L. J. Pandya and B. D. Tilak, *Chem. & Ind.* 981 (1958).
[22] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res., India* **14B**, 132 (1955); **15B**, 497 (1956).
[23] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 573 (1956).

XIV

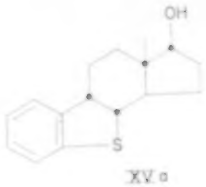



XV

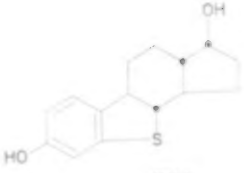



XIV a, R=H

XIV b, R=OH




XV a




XV b

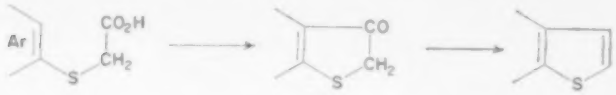
The carcinogenicity of some of the thiosters which do not contain a phenanthrene-bridge cannot be fitted into the K-region hypothesis and it seems likely that the sulphur atoms in these condensed thiophenes have their own characteristic reactivity towards a biological substrate. A study of the metabolism of the above condensed thiophenes is undoubtedly an important aspect which needs to be investigated in order to study the comparative biological activity of thiosters and their hydrocarbon counterparts, and to find out whether the sulphur atom is implicated in metabolism. Experimental support to the latter suggestion is forthcoming from the recent studies on the metabolism of dibenzothiophene (given orally to rats through diet) when 2-hydroxy-dibenzothiophene-5,5-dioxide was isolated (from urine).[24]

*Synthesis of condensed thiophenes.* The synthesis of thiosters of carcinogenic hydrocarbons necessitated exploration of new and better synthetical approaches to condensed thiophene ring system. Prior to the present work[3,25] perhaps the best method for the synthesis of thionaphthene and its derivatives (where the thiophene ring was located at the end of the fused ring system) consisted in cyclodehydration of arylthioglycolic acids (XVI) to corresponding thioindoxyls (XVII), followed by reduction of the latter to the corresponding thionaphthenes (XVIII).[25]

The above method is not very satisfactory, because of low yields in the cyclo-dehydration and reduction steps and the susceptibility of the thioindoxyls to air oxidation (conversion to thioindigo dyes).

Hartough and Meisel's survey of the literature on the subject[26] reveals ample

[24] T. B. Panse and B. D. Tilak, Unpublished work.
[25] B. D. Tilak, *Proc. Indian Acad. Sci.* **32A**, 390 (1950).
[26] H. D. Hartough and S. L. Meisel, *Compounds with Condensed Thiophene Rings*. Interscience, New York (1954).




XVI XVII XVIII

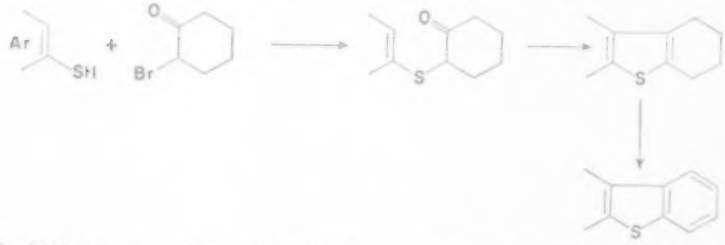
opportunities for contributions in the field of condensed thiophenes. The present paper gives a summary of the several new and general methods for the synthesis of condensed thiophenes developed by the author.

*Synthesis of condensed thiophenes from arylthiols*

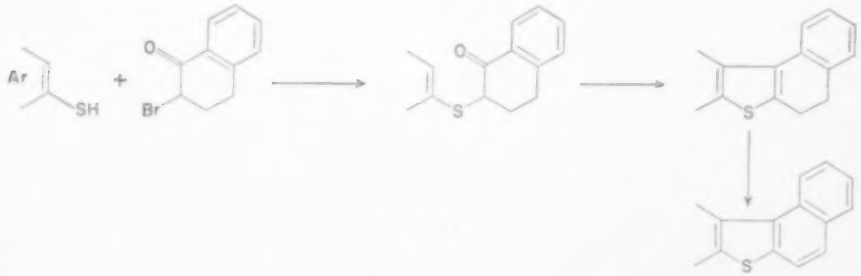
One or more thiophene, thiapyran, thionaphthene and naphthothiophene ring systems were fused to an aromatic residue by starting from aryl mono- and di-thiols on the one hand and halogenoacetaldehyde dialkyl acetals[3,25] and α-halogenocyclic ketones (2-bromocyclohexanone[27] and 2-bromo-1-tetralone[17]) on the other. These approaches may be summarized as follows:

*Method* I: *Fusion of one or more thiophene or thiapyran rings to an aryl residue*[3,25]

*Method* II: *Fusion of benzothiophene ring system to an aryl residue*[27]




*Method* III: *Fusion of a naphthothiophene ring system to an aryl residue*[17]




[27] K. Rabindran and B. D. Tilak, *Curr. Sci.* **20**, 207 (1951); *Proc. Indian Acad. Sci.* **36A**, 411 (1952).

TABLE 1. CONDENSED THIOPHENES FROM ARYL THIOLS AND HALOGENOACETALDEHYDE-DIALKYL ACETALS (Method I)*

| No. | Aryl ω-dimethoxyethyl sulphide | % Yield from thiol | Condensed thiophenes | % Yield from sulphide | Ref. |
|---|---|---|---|---|---|
| 1 | Phenyl ω-dimethoxyethyl sulphide | 76 | Thionaphthene | 37 | 3, 25 |
| | | | | 89 | 28 |
| 2 | Phenyl ω-diethoxyethyl sulphide | — | Thionaphthene | 32 | 3, 25 |
| 3 | *p*-Tolyl ω-dimethoxyethyl sulphide | 65 | 5-Methylthionaphthene | 48 | 29 |
| 4 | *m*-Tolyl ω-dimethoxyethyl sulphide | 69 | 6-Methylthionaphthene | 42<br>78 | 29<br>28 |
| 5 | *o*-Tolyl ω-dimethoxyethyl sulphide | 69 | 7-Methylthionaphthene | 53 | 29 |
| 6 | *p*-Chlorophenyl ω-dimethoxy--ethyl sulphide | 69 | 5-Chlorothionaphthene | 43 | 29 |
| 7 | *m*-Chlorophenyl ω-dimethoxy-ethyl sulphide | 65 | 6-Chlorothionaphthene<br>4-Chlorothionaphthene | 32 | 29<br>29a |
| 8 | *o*-Chlorophenyl ω-dimethoxyethyl sulphide | 62 | 7-Chlorothionaphthene | 40 | 29 |
| 9 | *o*-Bromophenyl ω-dimethoxyethyl sulphide | 78 | 7-Bromothionaphthene | 72<br>75<br>(39) | 28<br>30 |
| 10 | *p*-Bromophenyl ω-dimethoxyethyl sulphide | 72 | 5-Bromothionapthene | 13 | 30 |
| 11 | *p*-Nitrophenyl ω-dimethoxyethyl sulphide | 68 | 5-Nitrothionaphthene | 12 | 30 |
| 12 | *o*-Nitrophenyl ω-dimethoxyethyl sulphide | | Did not cyclize | | 30 |
| 13 | *p*-Methoxyphenyl ω-dimethoxyethyl sulphide | 70 | 5-Methoxythio-naphthene | low | 31 |
| 14 | *m*-Methoxyphenyl ω-dimethoxyethyl sulphide | 74 | 6-Methoxythio-naphthene | crude<br>62 | 31 |
| 15 | *o*-Methoxyphenyl ω-dimethoxyethyl sulphide | 82 | 7-Methoxythio-naphthene | 18 | 31 |
| 16 | *p*-Ethoxyphenyl ω-dimethoxyethyl sulphide | 85 | 5-Ethoxythionaphthene | 15 | 31 |
| 17 | 3-Methoxy-4-methylphenyl ω-dimethoxyethyl sulphide | 84 | 6-Methoxy-5-methyl-thionaphthene | 64 | 31 |

* Where two yields are quoted for the same compound, the yield in brackets refers to yield of the purer compound. In all other cases, the yield figure relates to the pure compound.

[28] K. Rabindran and B. D. Tilak, *Curr. Sci.* **20**, 205 (1951).
[29] A. V. Sunthankar and B. D. Tilak, *Proc. Indian. Acad. Sci.* **32A**, 396 (1950).
[29a] C. Hansch and B. Schmidhalter, *J. Org. Chem.* **20**, 1056 (1955).
[30] K. Rabindran, A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.* **36A**, 405 (1952).
[31] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 35 (1951).

TABLE 1 (*contd.*)

| No. | Aryl ω-dimethoxyethyl sulphide | % Yield from thiol | Condensed thiophenes | % Yield from sulphide | Ref. |
|---|---|---|---|---|---|
| 18 | β-Naphthyl ω-dimethoxyethyl sulphide | 40 | 4:5-Benzothionaphthene | 54 | 20 |
| 19 | α-Naphthyl ω-Dimethoxyethyl sulphide | 69 | Naphtho-(1′,8′-*bc*)-thiapyran (8%) and 6:7-benzothionaphthene (92%) | 53 (Mixtr.) | 20 32 |
| 20 | 8-Chloro-1-naphthyl ω-dimethoxyethyl sulphide | 70 | 3′-Chlorobenzo-(1′:2′, 6:7)-thionaphthene | 82 Crude | 33 |
| 21 | 2-Chloro-1-naphthyl ω-dimethoxyethyl sulphide | 72 | 9-Chloronaphtho-(1′,8′-*bc*) thiapyran. | 11 | 32,33 |
| 22 | 3-Phenanthryl ω-dimethoxyethyl sulphide | | 7:8-Benzothiophanthrene | 36 | 34 |
| 23 | 3-Thienyl ω-dimethoxyethyl sulphide | 66 | Thieno-(3,2-*b*) thiophene | 18 | 35,36 |
| 24 | 2-Thienyl ω-dimethoxyethyl sulphide | 73 | Thieno-(2,3-*b*) thiophene | 46 (18) | 35,36 |
| 25 | ω-Dimethoxyethyl 2-thionaphthenyl sulphide | 70 | Thieno-(2,3-*b*)-thionaphthene | 48 | 18 |
| 26 | 1,2-Bis-ω-dimethoxyethyl-mercaptobenzene | 70 | Benzo-(2,1-*b*,3,4-*b*′)-dithiophene | Poor | 11 |
| 27 | 4-Bromo-1,2-bis-ω-dimethoxyethylmercaptobenzene | 48 | 4-Bromobenzo-(2,1-*b*,3,4-*b*′) dithiophene | 7 | 11 |
| 28 | 1,3-Bis-ω-dimethoxyethyl-mercaptobenzene | 66 | Benzo-(1,2-*b*,5,4-*b*′)-dithiophene (41%) + Benzo-(1,2-*b*,3,4-*b*′)-dithiophene (59%) | 50 (Mixtr.) | 37 |
| 29 | 1-Chloro-2,4-bis-ω-dimethoxyethylmercaptobenzene | 72 | 8-Chlorobenzo-(1,2-*b*,3,4-*b*′)-dithiophene | 45 | 37 |
| 30 | 1,4-Bis-ω-dimethoxyethyl-mercaptobenzene | 52 | Benzo-(1,2-*b*,4,3-*b*′)-dithiophene | 32 (23) | 38 |
| 31 | 1,4-Dichloro-2,5-bis-ω-dimethoxyethylmercaptobenzene | 83 crude | 4,8-Dichlorobenzo-(1,2-*b*,4,5-*b*′)-dithiophene | 54 | 38 |
| 32 | 1,3-Di-(ω-dimethoxyethyl-mercapto)-naphthalene | 88 | Naphtho-(1,2-*b*,3,4-*b*′)-dithiophene, m.p. 169° | 80 | 39 |

[82] H. S. Desai, D. S. Rao and B. D. Tilak, *Chem. & Ind.* 464 (1957).
[83] V. K. Dikshit and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 78 (1951).
[84] B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 85 (1951).
[85] V. V. Ghaisas and B. D. Tilak, *Curr. Sci.* **22**, 184 (1953).
[86] V. V. Ghaisas and B. D. Tilak, *Proc. Indian Acad. Sci.* **39A**, 14 (1954).
[87] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **13B**, 829 (1954).
[88] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 65 (1957).
[89] H. S. Desai and B. D. Tilak, Unpublished work

TABLE 1 (*contd.*)

| No. | Aryl ω-dimethoxyethyl sulphide | % Yield from thiol | Condensed thiophenes | % Yield from sulphide | Ref. |
|---|---|---|---|---|---|
| 33 | 1,4-Di-(ω-dimethoxyethyl-mercapto)-naphthalene | 80 | Naphtho-(1,2-*b*,4,3-*b'*) dithiophene m.p. 134° | 8 | 39 |
| 34 | 1,5-Di-(ω-dimethoxyethyl-mercapto)-naphthalene | 38 | 1,6-Dithiopyrene Naphtho-(1',8'-*bc*, 5',4'-*b'c'*)-dithiapyran | 7 | 20,39 |
| 35 | 2,6-Di-(ω-dimethoxyethyl-mercapto)-naphthalene | 51 | Naphtho-(2,1-*b*,6,5-*b'*)-dithiophene | 20 | 20 |
| 36 | 2,7-Di-(ω-dimethoxyethyl-mercapto)-naphthalene | 77 | Naphtho-(2,1-*b*,7,8-*b'*)-dithiophene | 29 | 15 |
| 37 | 4-ω-Dimethoxyethyldiphenyl sulphide | 78 | 5-Phenylthionaphthene m.p. 100° | 79 | 40 |
| 38 | 4,4'-Di-(ω-dimethoxyethyl-mercapto)-diphenyl ether | 42 | 5,5'-Dithionaphthenyl ether, m.p. 93° | 10 | 40 |

The condensed thiophenes and thiapyrans synthesized by methods I, II and III are tabulated in Tables 1, 2 and 3 respectively which include reference to their preparation. Melting points and boiling points of hitherto unreported condensed thiophenes are also included in Tables 1–3 and other tables that follow.

*Scope and limitation of Methods* I, II *and* III. The general applicability of the methods for the synthesis of condensed thiophenes will be obvious from the large number of compounds synthesized (Tables 1–3). The only requisite for fusing a thiophene or a condensed thiophene ring system appear to be an aryl thiol with free *o* or *peri* position to enable cyclization of the thioglycolic-acetaldehyde dialkyl acetal side chain in Method I or the cyclodehydration of the 2-arylmercapto-cycloalkanones in Methods II and III.

The scope of Method I in the substituted thionaphthenes appears to be largely limited to 5-, 6-, and 7- substituted derivatives[4] although in one instance, 4-chloro-thionaphthene[29,29a] has also been prepared by this method. It may be mentioned that prior to the developement of Method I, only very few substituted thionaphthenes with substituents in the benzene half of the molecule were known. The latter type of thionaphthenes where the substituent is Cl, Br, O Me, Me, Et are now readily synthesizable by Method I. When the substituent was a nitro group, the yield of the thionaphthene was very low.[30] Other thionaphthenes containing substituents such as, hydroxy,[31] amino,[30] cyano[41] and carboxy[42] groups were then synthesized, starting from suitably substituted thionaphthenes prepared by Method I. Starting with aryl dithiols two thiophene rings have been fused to a benzene or naphthalene ring. In the case of α-thionaphthol, the end products were 6:7-benzothionaphthene and naphtho-(1':8'-*bc*)-thiapyran.[32] Naphthalene-1,5-dithiol likewise gave a bis-thiapyran.[20,39] With the exception of a recently described thiapyran,[42] these compounds appear to be

[40] L. J. Pandya, D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 516 (1959).
[41] R. B. Mitra, K. Rabindran and B. D. Tilak, *J. Sci. Ind. Res., India* **15B**, 627 (1956).
[42] A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson and A. G. Osborne, *J. Amer. Chem. Soc.* **81**, 1255 (1959).

the only two examples of aromatic thiapyrans. Both are deeper in colour than the corresponding thiophenes and give characteristic black coloured picrates as against yellow, orange or red coloured picrates given by condensed thiophenes. The structure of the bis-thiapyran from naphthalene-1,5-dithiol suggested by the author has been questioned by Banfield *et al.*[43] However, since desulphurization of the product gave 1,5-diethylnaphthalene, the structure suggested by the author is undoubtedly correct.[39] It is, however, interesting to record that cyclization of 1,5-di-acetonyl-mercaptonaphthalene gave exclusively 3,8-dimethyl-(6,7:7′,6′)-dithionaphthene, no thiapyran being detected. Similarly naphthalene-1,4-dithiol and naphthalene-1,3-dithiol also led to naphtho-(1:2-*b*,4,3-*b*′)-dithiophene and naphtho-(1:2-*b*,3:4-*b*′)-dithiophene respectively (Table 1). The structure of the latter compounds was proved by desulphurization and identification of the corresponding diethylnaphthalenes.[39] Method I is applicable to thiols derived from both, homocyclic as well as heterocyclic aromatic compounds such as, thiophene and thionaphthene, although ω-dimethoxy-ethyl 2-pyridyl sulphide failed to cyclize on treatment with PPA as discussed later.[29,49] In majority of cases the method has led to condensed thiophenes of unambiguous structure, but where more than one possibility exists as regards the direction of cyclization of the sulphide side chain, the structures of the resulting condensed thiophenes have been proved either by suitable degradations (desulphurization, oxidation, etc.) or by unambiguous synthesis (e.g. by blocking alternative cyclization positions by means of chlorine and dechlorination at a later stage).

Cyclization of the sulphide chain carrying the acetal group is best effected by the action of polyphosphoric acid (freshly prepared by mixing $P_2O_5$ and $H_3PO_4$) under reduced pressure or at atmospheric pressure in the presence or absence of boiling solvents such as, benzene, chlorobenzene or *o*-dichlorobenzene. Banfield *et al.*[43] have have used stannic chloride in chlorobenzene for the cyclization of acetals but they also found that PPA gave higher yields of the condensed thiophenes.

A series of condensed thionaphthenes and benzothionaphthenes have become available as a result of Methods II and III. Several of these compounds are of interest in the study of the chemical carcinogenesis discussed earlier in this paper. Whereas in Method I, thiophene or thiapyran rings are fused at the end of an aromatic ring system, in Methods II and III, benzothiophene or naphthothiophene rings are so fused. As against two steps involved in Method I, Methods II and III require three steps (condensation, cyclodehydration and dehydrogenation) for the conversion of arylthiols to condensed thiophenes. The yields in all the three steps are generally satisfactory. The scope and limitations of these methods are nearly the same as those for Method I. However, as against Method I, α-thionaphthol and naphthalene-1,5-dithiols did not lead to condensed thiapyrans[16,39] but to condensed thiophenes. The problems in structure determination were the same as in Method I and were dealt with similarly. As against the stability of halogenoacetaldehyde dialkyl acetals, 2-bromo-cyclohexanone is unstable and has to be freshly prepared and immediately used for condensation with arylthiols. This condensation is effected in aqueous alkali or in ethanolic sodium ethoxide. An alternative method consists in the use of pyridine

[43] J. E. Banfield, W. Davies, B. C. Ennis, S. Middleton and Q. N. Porter, *J. Chem. Soc.* 2607 (1956).
[44] M. K. Bhattacharjee and B. D. Tilak, Unpublished work.
[45] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 557 (1953).
[46] L. J. Pandya, Ph.D. (Tech.) Thesis University of Bombay (1959).
[47] G. R. N. Sastry and B. D. Tilak, Unpublished work.

TABLE 2. CONDENSED THIOPHENES FROM ARYL THIOLS AND BROMOCYCLOHEXANONE
(Method II)

| No. | 2-Arylmercaptocyclohexanones | % Yield from thiol | Reduced condensed thiophenes | % Yield from 2-arylmercapto cyclohexanone | Condensed thiophene | % Yield from reduced condensed thiophene | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | 2-Phenylmercaptocyclohexanones | 77 | 1,2,3,4-Tetrahydrodibenzothiophene | 74 | Dibenzothiophene | 91 | 27 |
| 2 | 2-(4′-Methylphenylmercapto)-cyclohexanone | 68 | 2-Methyl-6,7,8,9-tetrahydrodibenzothiophene | 60 | 2-Methyldibenzothiophene | 46 | 27 |
| 3 | 2-(3′Methylphenylmercapto)-cyclohexanone | 80 | 3-Methyl-6,7,8,9-tetrahydrothiophene | 78 | 3-Methyldibenzothiophene | 79 | 27 |
| 4 | 2-(2′-Methylphenylmercapto)-cyclohexanone | 85 | 4-Methyl-6,7,8,9-tetrahydrodibenzothiophene | 62 | 4-Methyldibenzothiophene | 51 | 27 |
| 5 | 2-(4′-Methoxyphenylmercapto)-cyclohexanone | 75 | 2-Methoxy-6,7,8,9-tetrahydrodibenzothiophene | low | — | — | 27 |
| 6 | 2-(3′-Methoxyphenylmercapto)-cyclohexanone | 50 | 3-Methoxy-6,7,8,9-tetrahydrodibenzothiophene, b.p. 155° (bath temp)/0·5 mm | 70 | 3-Methoxydibenzothiophene, m.p. 85° | 30 | 44 |
| 7 | 2-(2′-Methoxyphenylmercapto)-cyclohexanone | 77 | 4-Methoxy-6,7,8,9-tetrahydrodibenzothiophene | 47 | 4-Methoxydibenzothiophene | 30 | 27 |
| 8 | 2-(4′-Nitrophenylmercapto)-cyclohexanone | 92 | Did not cyclize | — | — | — | 27 |
| 9 | 2-(2′-Chlorophenylmercapto)-cyclohexanone | 75 | 4-Chloro-6,7,8,9-tetrahydrodibenzothiophene | 56 | 4-Chlorodibenzothiophene | 75 | 41 |
| 10 | 2-α-Naphthylmercaptocyclohexanone | 87 | 1,2-Benzo-5,6,7,8-tetrahydrothiafluorene | 70 | 1,2-Benzo-9-thiafluorene | 90 | 16 |
| 11 | 2-(8′-Chloro-1′-naphthylmercapto)-cyclohexanone | 99 | 1,2-(3′Chloro-2′,1′-benzo)-5,6,7,8-tetrahydro-9-thiafluorene | 66 | Se 1:2-Benzo-9-thiafluorene<br>NBS 1,2-(3′-chloro-2′,1′-benzo)-9-thiafluorene | 87 | 16<br>45 |
| 12 | 2-(β-Naphthylmercapto)-cyclohexanone | 93 | 3,4-Benzo-5,6,7,8-tetrahydro-9-thiafluorene, $P_2O_5$<br>$P_2O_5$ in boiling benzene<br>Vacuum distillation | 38<br>82<br>47 | 3,4-Benzo-9-thiafluorene | Se → 100<br>NBS → 65 | 16 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | 2-(3′-Thienylmercapto)-cyclohexanone | | 5,6,7,8-Tetrahydrothieno-(3,2-*b*)-thionaphthene | | Thieno-(3,2-*b*)-thionaphthene | 80 | 35,36 |
| 14 | 2-(2′-Thienylmercapto)-cyclohexanone | 81 | 4,5,6,7-Tetrahydrothieno-(2,3-*b*)-thionaphthene | 44 | Thieno-(2,3-*b*)-thionaphthene | | 35,36 |
| 15 | 2-(3′-Thionaphthenyl-mercapto)-cyclohexanone | | 1,2,3,4-Tetrahydrothio-naphtheno-(3,2-*b*)-thio-naphthene | | Thionaphtheno-(3,2-*b*)-thionaphthene | | 46<br>19 |
| 16 | 2-(2′-Thionaphthenyl-mercapto)-cyclohexanone | 95 | 1,2,3,4-Tetrahydrothio-naphtheno-(2,3-*b*)-thio-naphthene | 70 | Thionaphtheno-(2,3-*b*)-thionaphthene | 61 | 18 |
| 17 | *m*-Di-(2-oxo-cyclohexyl-mercapto)-benzene | 55 | 1,2,3,4,6,7,8,9-Octahydro benzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene | 56 | Benzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene | 46 | 37 |
| 18 | 1-Chloro-2,4-di-(2′-oxo-cyclohexylmercapto)-benzene | 55 | 11-Chloro-1,2,3,4,6,7,8,9-octahydrobenzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene | 46 | Benzo-(1,2-*b*,3,4′-*b*′)-dithionaphthene | | 37 |
| 19 | *p*-Di-(2-oxo-cyclohexyl-mercapto)-benzene | 73 | A mixture of 1,2,3,4,7,8,9,10-octahydrobenzo-(1,2-*b*, 4,5-*b*′) dithionaphthene (9%) and 1,2,3,4,9,10,11,12-Octahydro-benzo-(1,2-*b*, 4,3-*b*′)-dithionaphthene (10%) | 64 (Mixture) | Benzo-(1,2-*b*,4,5-*b*′)-dithionaphthene (24%) and Benzo-(1,2-*b*, 4,3-*b*′)-dithionaphthene (33%) | | 11 |
| 20 | 1,4-Dichloro-2,5-di-(2-oxo-cyclohexylmercapto)-benzene | 53 | 6,12-Dichloro-1,2,3,4,7,8,9,10-octahydrobenzo-(1,2-*b*, 4,5-*b*′)-dithionaphthene | 43 | Benzo-(1,2-*b*, 4,5-*b*′)-dithionaphthene | 44 | 11 |
| 21 | 1,3-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene | 87 | 1,2,3,4,6,7,8,9-Octahydronaphtho (2,1-*b*, 4,3-*b*′)-dithio-naphthene. m.p. 152°-5 | 72 | Naphtho-(2,1-*b* 4,3-*b*′)-dithionaphthene m.p. 221° | 92 | 39 |
| 22 | 1,4-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene | | 1,2,3,4,5,6,7,8-Octahydro-naphtho-(1,2-*b*, 4,3-*b*′)-dithionaphthene, m.p. 225·5° | | Naphtho-(1,2-*b*, 4,3-*b*′)-dithionaphthene, m.p. 215° | | 39 |
| 23 | 1,5-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene, m.p. 194° | 94 | 1,2,3,4,8,9,10,11-Octahydro-naphtho-(1,2-*b*, 5,6-*b*′)-dithionaphthene, m.p. 325° | 44 | Naphtho-(1,2-*b*, 5,6-*b*′)-dithionaphthene. m.p. > 360° | 80 | 39 |

TABLE 3.—CONDENSED THIOPHENES FROM ARYL THIOLS AND 2-BROMO-1-TETRALONE

| No. | 2-Arylmercapto-1-tetralones | % Yield from thiol | Dihydro derivatives of condensed thiophenes | % Yield from 2-aryl mercapto-1-tetralone | Condensed thiophenes | % Yield from the dihydro derivative | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | 2-Phenylmercapto-1-tetralone | 83 | 1,2-Dihydro-3,4-benzo-9-thiafluorene | 94 | 3,4-Benzo-9-thiafluorene | 95 | 17 |
| 2 | 2-(2′-Naphthylmercapto)-1-tetralone | 88 | 1,2-Dihydro-3,4,5,6-dibenzo-9-thiafluorene | 97 | 3,4,5,6-Dibenzo-9-thiafluorene | 92 | 17 |
| 3 | 2-(1′-Naphthylmercapto)-1-tetralone | 92 | 1,2-Dihydro-3,4,7,8-dibenzo-9-thiafluorene | 96 | 1,2,5,6-Dibenzo-9-thiafluorene | 86 | 17 |

which was employed in the condensation of thiophenol[47] and naphthalene-1,5-dithiol.[39] Cyclodehydration of the 2-arylmercaptocycloalkanones was generally effected by the action of the following reagents: (1) $P_2O_5$ at 160–180°, (2) $P_2O_5$–$H_3PO_4$ mixture at 175–190° in vacuum or at atmospheric pressure, (3) $P_2O_5$ in boiling benzene or chlorobenzene. The hydroaromatic condensed thiophenes obtained were dehydrogenated by several agents, although treatment with selenium at 300–350° gave best results.[45]

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TABLE 4.—CONDENSED THIOPHENES FROM DIARYLS
(Method IV)

| No. | Diaryls used | Condensed thiophenes obtained by thionation | % Yield | Ref |
|---|---|---|---|---|
| 1 | *p*-Terphenyl | Benzo-(1,2-*b*,4,5-*b'*)-dithionaphthene (18%) | 22 (Mixture) | 11 |
| | | Benzo-(2,1-*b*,3,4-*b'*)-dithionaphthene (27%) | | |
| 2 | *m*-Terphenyl | Benzo-(1,2-*b*, 5,4-*b'*)-dithionaphthene | | 14 |
| | | Benzo-(1,2-*b*, 3,4-*b'*)-dithionaphthene | | |
| | | Benzo-(1,2-*b*, 4,5-*b'*)-dithionaphthene | | |
| 3 | 2:2′-Dithionaphthenyl | Thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene | | 14 |
| 4 | 3:3′-Dithionaphthenyl | Compound (A), m.p. 190°, + thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene (in presence of $AlCl_3$) compound m.p. 200° (without $AlCl_3$) | | 14,46 |
| 5 | 2:3′-Dithionaphthenyl | Compound (A), m.p. 190°, + thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene | | 14,46 |
| 6 | 3-Phenylthionaphthene | Thionaphtheno-(3,2-*b*)-thionaphthene (in presence of $AlCl_3$) | 7 | 19,48 |
| | | Thionaphtheno-(2,3-*b*)-thionaphthene (without $AlCl_3$) | 20 | 18,48 |

*Synthesis of condensed thiophenes from diaryls.*[11,14] Among the different methods available for the synthesis of condensed thiophenes, the one step synthesis from diaryls by interaction with sulphur and anhydrous aluminium chloride is an attractive route which does not appear to have been much studied. The approach (Method IV) has now been studied in the case of 2 and 3-phenyl thionaphthenes; *meta*- and *para*-terphenyls, 2,2′-,3,3′-, and 2,3′-dithionaphthenyls and the results obtained are summarized in Table 4.

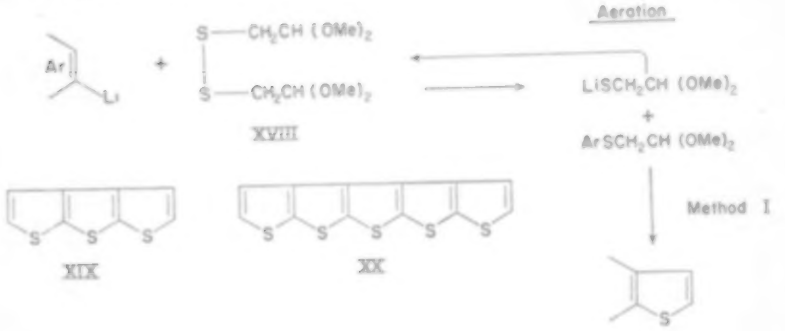
*Method* IV. Aluminium chloride used in the thionation effects partial isomerization of the diaryls. Several isomeric condensed thiophenes are, therefore, formed in the above synthesis and the structures of the condensed thiophenes so obtained have to be proved in each case. In the latter connection, aluminium chloride induced

isomerization of the diaryls has also to be studied. In spite of these limitations, this route is still attractive, since the condensed thiophenes which result are often otherwise difficultly accessible, and also because the mixture of the isomeric condensed thiophenes is easily separable. The method, however, suffers from low yield of the thionation products.

Very recently 3-phenylthionaphthene has been converted to thionaphtheno-(2:3-*b*)-thionaphthene by thionation with sulphur alone and it appears that aluminium chloride-induced isomerizations can thus be avoided.[48] In fact when this thionation was carried out in presence of aluminium chloride, the isomer thionaphtheno-(3:2-*b*)-thionaphthene was obtained, whereas 2-phenylthionaphthene when treated with sulphur and aluminium chloride did not yield the above condensed thiophene.[48]

Method IV is likely to prove of general interest and with this end in view synthesis of several diaryls containing benzene, thiophene, naphthalene and thionaphthene ring systems has been undertaken in this laboratory as discussed later (Method VII).

*Synthesis of condensed thiophenes from aryllithium derivatives* (Method V). A novel and general synthesis (Method V) of aryl $\omega$-dimethoxyethyl sulphides dispenses with the need of starting with thiols (foul smelling!) required in the synthesis of condensed thiophenes by Method I discussed earlier.[21,49] The method may be outlined as follows:




*Method* V. The above method has led to the synthesis of the known condensed thiophenes such as thionaphthene, thieno-(2:3-*b*)-thiophene, naphtho-(1′:8′-*bc*)-thiapyran, 6:7-benzothionaphthene, and thieno-(2:3-*b*)-thionaphthene, in addition to the hitherto inaccessible condensed thiophenes: thieno-(3:4-*b*, 5:4-*b*′) dithiophene (XIX) and thieno-(3:4-*b*)-pyrene (XIIA, the thioster of the potent carcinogen 3:4-benzpyrene). Compounds prepared by the method are listed in Table 5. This synthesis opens a possible route to thiosters of polycenes, since the process of metalation and interaction with XVIII may be repeated on XIX, leading ultimately to the pentacene analogue XX. However, the bond angles of the sulphur atom linked in these compounds will be so much deviated from those in thiophene, that a *cis*-build up of thiophene rings beyond the tetra or pentacyclic stage may be very difficult if not impossible. A pentacene analogue containing five *cis*-fused thiophene rings (XX) could be built up with a Courtauld model[50] with adjustable bonds, but the molecule was highly strained. Attempts at the synthesis of a pentacene analogue have already

[48] T. S. Murthy and B. D. Tilak, Unpublished work.
[49] L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 371 (1959).
[50] R. Robinson, *Disc. Faraday Soc.* **16**, 125 (1954).

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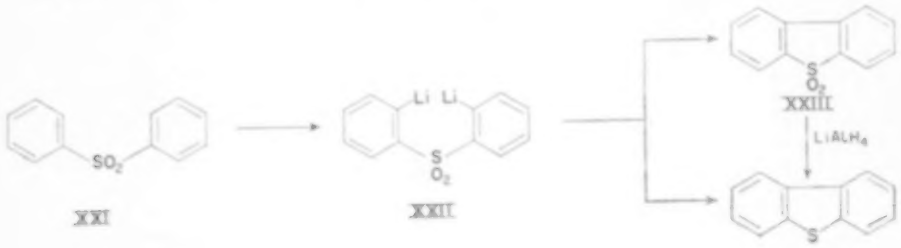
TABLE 5. CONDENSED THIOPHENES FROM ARYLLITHIUM DERIVATIVES

| No. | Starting materials | Aryllithium derivative | Aryl ω-dimethoxyethyl sulphide (acetal) | % Yield from the starting material | Condensed thiophenes | % Yield from the acetal | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | Bromobenzene | Phenyllithium | ω-Dimethoxyethyl phenyl sulphide | 97 | Thionaphthene | 41 | 21,49 |
| 2 | Thiophene | 2-Thienyllithium | ω-Dimethoxyethyl 2-thienyl sulphide | 42 | Thieno-(2,3-*b*)-thiophene | 11 | 21,49 |
| 3 | α-Bromonaphthalene | α-Naphthyllithium | ω-Dimethoxyethyl α-naphthyl sulphide | 45 | A mixture of naphtho-(1',8'-*bc*)-thiapyran and 6,7-benzothio-naphthene. | 34 | 21,49 |
| 4 | Thionaphthene | 2-Thionaphthenyl-lithium | ω-Dimethoxyethyl 2-thio-naphthenyl sulphide | 69 | Thieno-(2,3-*b*)-thio-naphthene | 36 | 21,49 |
| 5 | 2-Bromopyridine | 2-Pyridyllithium | ω-Dimethoxyethyl 2-pyridyl sulphide | 54 | Did not cyclize | — | 21,49 |
| 6 | 2,5-Di-iodothiophene | Thienyl-2,5-dilithium | 2,5-Bis-ω-dimethoxyethyl-mercaptothiophene | 58 | Thieno-(2,3-*b*,5,4-*b'*) dithiophene | 33 | 21,49 |
| 7 | 3-Bromopyrene | 3-Pyrenyllithium | ω-Dimethoxyethyl 3-pyrenyl sulphide | | Thieno-(3,4-*b*)-pyrene | low | 21,49 |

been undertaken, as also the synthesis of a dithiophene analogue of 3:4,9:10-dibenzpyrene (the suspected carcinogenic factor in tobacco tar)[51] starting from 3,10-dibromopyrene.

*Synthesis of condensed thiophenes from diaryl sulphones.* A few condensed thiophenes have been synthesized by the cyclization of diaryl sulphides by the action of arylsodium and/or aryllithium[52] derivatives, and by the action of sodium amide on diaryl sulphoxides.[53] In view of the formation of diphenyl sulphone-2,2′-dilithium (XXII) from diphenyl sulphone (XXI)[54] and the synthesis of 2,2′- and 3,3′-dithionaphthenyls from 2- and 3-bromothionaphthenes by the action of cupric chloride on the corresponding Grignard reagents,[40] the possibility of cyclization of XXII by interaction with cupric chloride was investigated. It is of interest to record that a little of dibenzothiophene was formed along with the expected sulphone XXIII (yield 70%). The latter was then readily converted to dibenzothiophene in good yield by reduction with lithium aluminium hydride.[55] This synthesis (Method VI) may also prove to be of general interest for the preparation of other condensed thiophenes from diaryl sulphones as well as for the synthesis of dialkyls, diaryls, and diarylenes.

Experiments in this direction have been already undertaken.



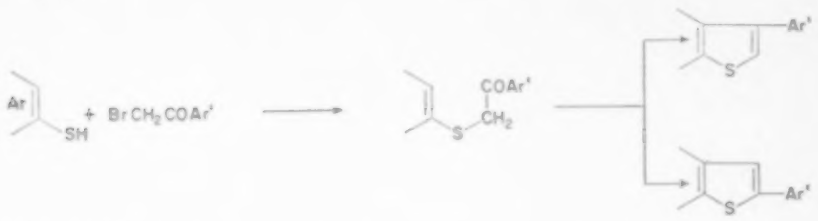

XXI XXII XXIII

*Method* VI: *Synthesis of alkyl and aryl derivatives of condensed thiophenes* (Method VII). Synthesis of 3-alkyl and 2,3-dialkyl thionaphthenes by cyclodehydration of aryl 2-ketoalkyl sulphides (Ar—S—CHR—CO—R′) has been reported by Werner.[56] Banfield *et al.*[57] have suggested that cyclodehydration of sulphides represented by the general formula Ar—S—$CH_2$—CO—R leads to 3-alkylthionaphthenes, where R is an alkyl group, and to 2-arylthionaphthenes where R is an aryl group. A re-investigation of Banfield's work has revealed that both 2-aryl and 3-aryl thionaphthenes were formed when aryl aroylmethyl sulphides were treated with polyphosphoric acid at 170–180°.[58] The structure of 3-arylthionaphthenes was proved by two unambiguous synthesis involving the Grignard reaction: (1) starting from 3-halo-(iodo or bromo) thionaphthene (and related compounds) and cyclohexanones[58]

[51] B. D. Tilak, M. K. Unni and K. Venkataraman, *Tetrahedron* **3**, 62 (1958).
[52] *a* A. Luttringhous, G. Wagner, E. Sucker and G. Borth, *Liebigs Ann.* **557**, 54 (1945); *b* G. Wittig and E. Benz, *Chem. Ber.* **91**, 873 (1958).
[53] *a* J. H. Freeman and C. E. Scott, *J. Amer. Chem. Soc.* **77**, 3384 (1955); *b* H. Gilman and D. R. Swayampati, *J. Org. Chem.* **21**, 1273 (1956); *c* R. Wilputte, *Bull. Soc. Chem. Belg.* **65**, 674–698 (1956); *Chem. Abstr.* **51**, 6589$^c$ (1957).
[54] *a* W. E. Truce and M. F. Amos, *J. Amer. Chem. Soc.* **73**, 3013 (1951); *b* E. A. Lehto and D. A. Shirley, *J. Org. Chem.* **22**, 989 (1957).
[55] V. S. Palkar and B. D. Tilak, Unpublished work.
[56] E. G. G. Werner, *Rec. Trav. Chim.* **68**, 509 (1949).
[57] J. E. Banfield, W. Davies, N. W. Gamble and S. Middleton, *J. Chem. Soc.* 4791 (1956).
[58] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 77 (1959).

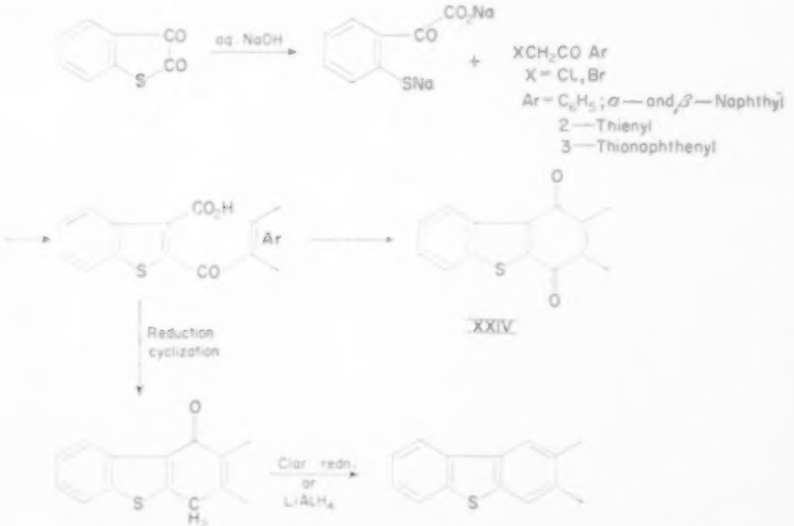
and (2) starting from thioindoxyl (and related compounds) and arylhalides (bromo or iodo).[48]

The 2-aryl and 3-aryl-thionaphthenes and related compounds which were synthesized by cyclodehydration of compounds of the type Ar—S—$CH_2$—COAr′ are listed in Table 6. The general method of synthesis (Method VII) may be represented as follows:




*Method* VII: A reaction mechanism to account for the formation of the two isomeric arylthionaphthenes in the above method has been suggested.[58] The relation between the yield of the two isomers and chemical structure of the intermediate sulphides is under investigation. Another point of interest in this study is the possible use of the arylthionaphthenes in the synthesis of condensed thiophenes by the Method IV discussed above.

*Synthesis of condensed thiophenes from thiophanthrenequinones and related compounds.* Thiophanthrenequinones and related benzo-derivatives were prepared from thioisatin as follows:




*Method* VIII. The above method was first suggested by Mayer[61] and was used subsequently by the author for the synthesis of several thiophanthrenequinones of the type XXIV,[3,4,10,15] which were required in the synthesis of *meso*-dimethyl derivatives. The latter compounds were required in the study of chemical carcinogenesis discussed earlier in the paper.

TABLE 6. SYNTHESIS OF ALKYL OR ARYLTHIONAPHTHENES FROM α-ARYLMERCAPTOKETONES

| No. | α-Arylmercaptoketones | % Yield from thiol | Alkyl or arylthionaphthenes | % Yield from α-aryl mercapto-ketone | Ref. |
|---|---|---|---|---|---|
| 1 | Phenyl phenacyl sulphide | 95 | 3-Phenylthionaphthene, | 15 | 58 |
| | | | 2-Phenylthionaphthene | 44 | 57,59 |
| 2 | *p*-Tolyl phenacyl sulphide | 86 | 5-Methyl-2-phenylthionaphthene, | 36 | 57 |
| | | | 5-Methyl-3-phenylthionaphthene. | 25 | 58 |
| 3 | α-Phenylmercaptopropiophenone | 82 | 2-Methyl-3-phenylthionaphthene, b.p. 110–115° (bath temp)/0·01 mm. | 82 | 48 |
| 4 | *p*-Methoxyphenacyl phenyl sulphide | 84 | 3-(*p*-Methoxyphenyl)-thionaphthene, b.p. 130–35° (bath temp)/0·01 mm. | 17 | 48 |
| | | | 2-(*p*-Methoxyphenyl)-thionaphthene | 34 | 57 |
| 5 | β-Naphthyl phenacyl sulphide | 66 | 3-Phenyl-4:5-benzothionaphthene, | 54 | 48,59 |
| | | | 2-Phenyl-4:5-benzothionaphthene. | 10 | |
| 6 | α-Naphthacyl phenyl sulphide | 80 | 3-(α-Naphthyl)-thionaphthene, m.p. 92° | 36 | 48 |
| | | | 2-(β-Naphthyl)-thionaphthene, m.p. 212° | 4 | 60 |
| 7 | β-Naphthacyl phenyl sulphide | 88 | 3-(β-Naphthyl)-thionaphthene, m.p. 60° | 38 | 48 |
| | | | 2-(β-Naphthyl)-thionaphthene, m.p. 212° | 13 | |
| 8 | 2-Thienoacetyl phenyl sulphide | 77 | 3-(2′-Thienyl)-thionaphthene, b.p. 160–65° (bath temp)/2·5 mm. | 32 | 48 |
| | | | 2-(2′-Thienyl)-thionaphthene, m.p. 156° | 16 | 40 |
| 9 | 2-Thionaphthacyl phenyl sulphide | 18 | 2,3′-Dithionaphthenyl, m.p. 76° | — | 40 |
| 10 | 3-Thionaphthacyl phenyl sulphide | 46 | 3,3′-Dithionaphthenyl, m.p. 85° | 16 | 40 |
| 11 | 2-Thionaphthenyl phenacyl sulphide | 72 | 3-Phenyl-thionaphthieno-(2,3-*b*)-thiophene, m.p. 78° | 90 | 48 |

Removal of the quinone group in the above thiophanthrenequinones by reduction appeared to be an attractive route for the synthesis of several condensed thiophenes which are of interest in the above study of chemical carcinogenesis. The reduction step, however, proved difficult, and with the exception of 2:3-benzo-4:9-thiophanthrenequinone which was reduced by zinc and ammonia in poor yield (cf. Mayer),[61] the other quinones were not amenable to reduction by means of milder methods such as, treatment with zinc and alkali, lithium aluminium hydride, two step reduction by conversion to anthrone and subsequent reduction by zinc and alkali. When a more drastic method of reduction such as zinc dust distillation was employed, the sulphur atom was removed (e.g. formation of 3-phenylphenanthrene from 2:3,7:8-dibenzo-4,9-thiophanthrenequinone[3]) and under milder conditions such as Clar reduction, the intermediate anthrones were obtained.[3,4] Recently two condensed thiophenes have been prepared in low yield by the reaction sequence outlined above (Method VIII).

By employing the above procedure, compounds VIA and VIIIA (see Chart I), the thiosters of the carcinogens 1:2,5:6-dibenzanthracene and 1:2,7:8-dibenzanthracene, have been prepared in low yield.[13] In view of the facile synthesis of anthrones [either through the diarylmethane-*o*-carboxylic acids (as outlined above) or by reduction of quinones], the above method of removal of the quinone groups may prove of general interest. Thus anthraquinone and 2-methylanthraquinone have been reduced to anthracene and 2-methylanthracene through the corresponding anthrones, either by Clar reduction or by the action of lithium aluminium hydride.

Although the above synthetical methods for condensed thiophenes were initially developed in connection with the synthesis of thiosters of carcinogenic hydrocarbons, the work is also interesting in the study of the following:

(1) Precise nature and extent of isosterism between thiophene and benzene in their polycyclic derivatives,

(2) fine structure of fused thiophene ring systems,

(3) general chemistry of condensed thiophenes and

(4) nature of sulphur containing compounds in the higher boiling fractions of petroleum. Indeed, on account of the latter interest, major portion of the work on condensed thiophenes in progress over the last three years, has been financed, out of a generous grant from the Petroleum Research fund of the American Chemical Society. The condensed thiophenes are also being studied under the American Petroleum Institute Research Project 48, which deals with the synthesis, properties and identification of sulphur compounds in petroleum.

*Acknowledgements*—I am indebted to Sir Robert Robinson at whose suggestion the work was initiated in 1944 at Oxford. I am also grateful to my research colleagues whose work is referred to herein. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is hereby made to the donors of the said fund.

[59] O. Dann and Kokorudz, *Chem. Ber.* **91**, 172 (1958).
[60] R. Schuetz and L. Ciporin, *J. Org. Chem.* **23**, 206 (1958).
[61] F. Mayer, A. Mombour, W. Lassman, W. Werner, W. Laudmann P. and E. Schneider, *Liebigs Ann.* **485**, 259 (1931).

Tetrahedron, 1960, Vol. 9, pp. 96 to 105. Pergamon Press Ltd. Printed in Northern Ireland

# 4,5:12,13-DIBENZOHEPTAZETHRENE AND 5,6:8,9:14,15:17,18-TETRABENZOHEPTACENE

E. CLAR, G. S. FELL and (in part) M. H. RICHMOND
Department of Chemistry, The University of Glasgow

(*Received* 2 *November* 1959)

**Abstract**—Terephthalyl chloride and octahydrophenanthrene gave the diketone I which on pyrolysis yielded the tetradecahydro, octahydro, and dihydro-dibenzoheptazethrenes II, III, and IV respectively. The same hydrocarbons were obtained from the isomeric diketone V, involving a rearrangement. Dehydrogenation of the hydro derivatives or pyrolyses of the diketones in presence of copper powder gave the green dibenzoheptazethrene VI. This is a strongly basic hydrocarbon and forms stable salts VII. Oxidation formed the quinone IX. The dihydro compound IV added maleic anhydride twice, to give the dianhydride X, which cyclized in a sodium chloride-zinc chloride melt, to tetrabenzoheptacene XI. This is a fully benzenoid, orange hydrocarbon of very high stability.

TEREPHTHALYL chloride condensed twice with octahydrophenanthrene and aluminium chloride in an analogous way to benzoyl chloride with octahydrophenanthrene.[1] The diketone I was pyrolysed and dehydrogenated with copper powder. Owing to the sensitivity of the resulting dibenzoheptazethrene* the yield was rather poor. Better results were obtained without copper powder. The dihydro compound IV crystallized first from the diluted pyrolysate together with a little octahydro compound III. The tetradecahydro derivative II was obtained from the mother liquor by chromatography. The latter shows the absorption spectrum of a 1,2:5,6-dibenzanthracene derivative, as is demonstrated by comparison with 1,2:5,6-dibenzanthracene in Fig. 1. The absorption spectra of the dihydro and octahydro compounds IV and III respectively, are closely related to the spectrum of 2,3:7,8-dibenzoperinaphthene[1] as shown in Fig. 2. The two former being related to the latter as terephenyl is to diphenyl. These compounds cannot have a 1,2:5,6-dibenzanthracene complex as in II.

These hydro derivatives can be dehydrogenated with palladium charcoal to dibenzoheptazethrene VI. The dihydro compound was also easily dehydrogenated by a simple crystallization from nitrobenzene or with chloranil in boiling trichlorobenzene.

The diketone V obtained from isophthalyl chloride, octahydrophenanthrene, and aluminium chloride, gave the same hydro derivatives by rearrangement of the diketone during the pyrolysis. The rearrangement is always observed when the resulting hydrocarbon would have the 1,2:7,8-dibenzanthracene skeleton. This has never been obtained by the Elbs reaction. Compounds with the 1,2:5,6-dibenzanthracene structure are formed in its place.[2]

The best yield of the dihydro compound IV was recorded when pure octahydrophenanthrene was replaced by an excess of a technical product containing about 30 per cent tetrahydrophenanthrene.

* The name heptazethrene is derived from zethrene as used in E. Clar, *Aromatische Kohlenwasserstoffe* p. 393. Springer Verlag (1952).

[1] E. Clar, *Ber. Dtsch. Chem. Ges.* **76**, 611 (1943).

[2] J. W. Cook, *J. Chem. Soc.* 487 (1931); 1472 (1932); 499 (1931); E. Clar and Fr. John, *Ber. Dtsch. Chem. Ges.* **64**, 981 (1931); E. Clar, Fr. John and R. Avenarius, *Ber. Dtsch. Chem. Ges.* **72**, 2139 (1939); E. Clar, *Ber. Dtsch. Chem. Ges.* **73**, 81 (1940).

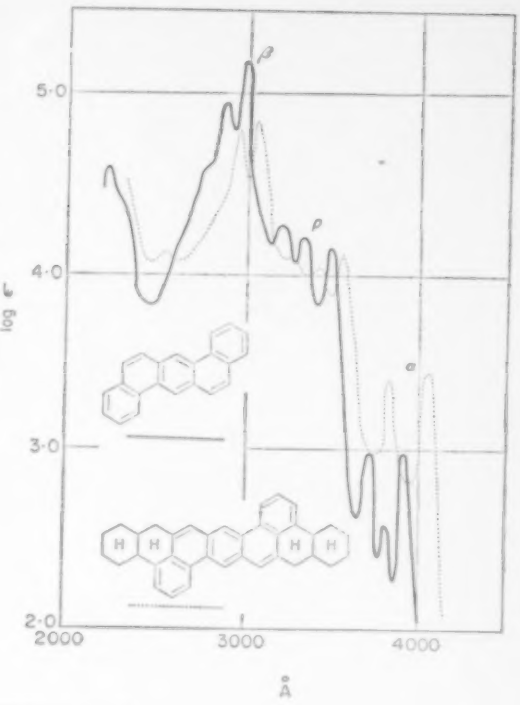



FIG. 1. Absorption max (Å) and log $\varepsilon$ (in parentheses) of:
(————) 1:2,5:6-Dibenzoanthracene, in benzene; α, 3950 (3·16), 3850 (2·70), 3730 (3·10); *p*, 3510 (4·24), 3365 (4·21), 3220 (4·32); β, 3000 (5·10), 2900 (4·93), in alcohol 2770 (4·72), 2300 (4·50).
(· · · · ·) Tetradecahydro-4:5,12:13-dibenzoheptazethrene (II) in benzene; α, 4100 (3·64), 3880 (3·60); *p*, 3600 (4·30), 3460 (4·26), 3300 (4·32); β, 3100 (4·98), in cyclohexane, 2970 (4·92), 2350 (4·74).

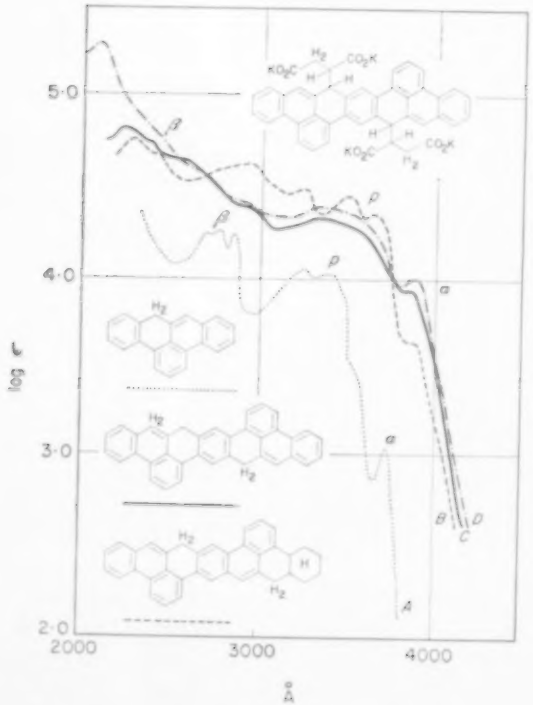



FIG. 2. Absorption max (Å) and log $\varepsilon$ (in parentheses) of:
(A) (· · · · ·) 2:3:7:8-Dibenzoperinaphthene in alcohol; α, 3720 (3·04); *p*, 3390 (4·02), 3270 (4·04), 3020 (4·84) β, 2850 (4·23), 2760 (4·24), 2690 (4·26).
(B) (– – – – –) Octahydro-(4:5,12:13)-Dibenzoheptazethrene (III) in benzene; α, 3840 (3·58); *p*, 3600 (4·31), 3440 (4·41), 3090 (4·44); in cyclohexane β, 2860 (4·58), 2110 (4·64).
(C) (————) 7,15-Dihydro-(4:5,12:13)-dibenzoheptazethrene (II) in benzene; α, 3900 (4·01); *p*, 3540 (4·32), 3400 (4·36); in cyclohexane α, 2530 (4·68), 2220 (4·84).
(D) (– · – · – · –) Tetrapotassium salt of (X), in 50% alcohol; α, 3860 (3·96); *q*, 3400 (4·40); α, 2100 (5·32).

Dibenzoheptazethrene VI has a green, shining surface and gives violet red, photo-oxidizable solutions. It forms an insoluble, stable, deep violet, hydrochloride, perchlorate and sulphate, giving a salt even with phosphoric acid VII. These basic properties can be explained by the polarized structure VIa, which has one more benzenoid ring (marked with circles) than structure VI, which shows four fixed double bonds in the centre, compared with two in zethrene.[3]

Suspensions of the hydrochloride gave the chloro derivative VIII, on standing in the presence of light and air. The same compound was easily obtained from the dihydro compound IV or dibenzoheptazethrene VI with phosphorus pentachloride in boiling xylene. Dibenzoheptazethrene VI and its chloro derivative VIII, can be readily reduced to the dihydro compound IV with boiling pyridine, acetic acid and zinc dust. Oxidation of dibenzoheptazethrene VI, or its derivative IV, with selenium dioxide in boiling nitrobenzene, gave the yellow quinone IX which does not form a vat with

[3] E. Clar, K. F. Lang and H. Schulz-Kiesow. *Chem. Ber.* **88**, 1520 (1955).

alkaline sodium dithionite solution. The absorption spectrum of dibenzoheptazethrene VI, and its chloro compound are shown in Fig. 3. The spectrum of the quinone IX is recorded in Fig. 4 in comparison with 2,3:7,8-dibenzoperinaphthone.[1]

Dihydrodibenzoheptazethrene IV condensed quantitively with maleic anhydride to the dianhydride X. The absorption spectrum of the corresponding tetracarboxylic acid (Fig. 2) is very closely related to the dihydro compound IV, thus indicating that no change in the aromatic conjugation had taken place.

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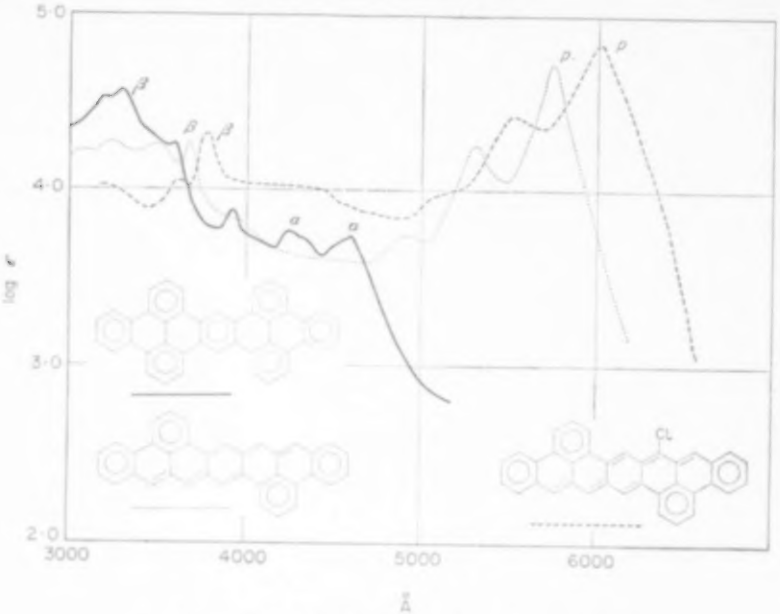



FIG. 3. Absorption max (Å) and log $\varepsilon$ (parentheses) of:
(· · · · ·) 4:5,12:13-Dibenzoheptazethrene (VI) in benzene, (intensities from trichlorobenzene): *p*, 5720 (4·70), 5280 (4·26), 4880 (3·74); $\beta$, 3640 (4·26).
(– – – –) 7-Chlorodibenzoheptazethrene (VIII) in trichlorobenzene; *p*, 6000 (4·83), 5500 (4·40), 5100 (3·98); $\beta$, 3780 (4·30).
(————) 5:6,8:9,14:15,17:18-Tetrabenzoheptacene (XI) in benzene (intensities from methyl naphthalene); $\alpha$, 4610 (3·70), 4260 (3·75); *p*, 3930 (3·86); $\beta$, 3290 (4·54).

The tetracarboxylic acid (derived from X) cyclized in a sodium chloride-zinc chloride melt, with simultaneous decarboxylation, to tetrabenzoheptacene XI. This is an orange hydrocarbon of high thermal stability, which does not dissolve in concentrated sulphuric acid, and shows a red phosphorescence of long life in solid ethanolic solution at 77°K (see Table 2). It does not react with maleic anhydride and shares these properties with other purely benzenoid hydrocarbons.[4] The chemical inertness of benzenoid hydrocarbons can be related to the fact that their U.V. spectra are the most strongly shifted to the violet among the spectra of the isomeric aromatic hydrocarbons, except for the corresponding polyphenyls with the same number of rings. Confirmation that benzenoid rings are the reason for the high stability and the extreme violet shift in the U.V. spectrum of such hydrocarbons is obtained by the comparison

[4] E. Clar and M. Zander, *J. Chem. Soc.* 1861 (1958); E. Clar and C. T. Ironside, *Proc. Chem. Soc.* 150 (1958); E. Clar, M. Zander and C. T. Ironside, *J. Chem. Soc.* 142 (1959); M. Zander, *Chem. Ber.* **92**, 2744 (1959).

in Fig. 3, where the spectrum of tetrabenzoheptacene XI is shown together with that of dibenzoheptazethrene VI. The spectrum of the fully benzenoid tetrabenzoheptacene XI is strongly shifted to the violet, although the hydrocarbon XI contains two more rings than dibenzoheptazethrene VI which is not fully benzenoid.

The structure XI is based on the assumption that a hydrocarbon with the maximum number of benzenoid rings is usually formed in preference to other ways of cyclization, which would yield hydrocarbons with fewer benzenoid rings. This would be contrary

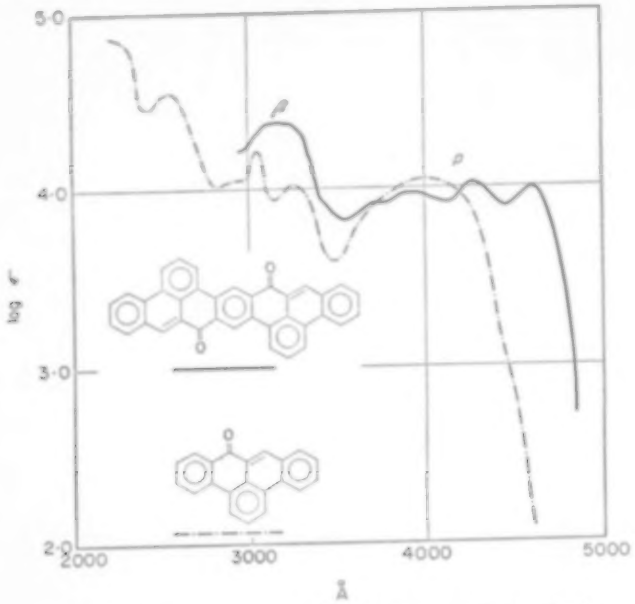



FIG. 4. Absorption max in (Å) and log $\varepsilon$ (in parentheses) of:
(————) 4:5,12:13-Dibenzoheptazethrene-7,15-quinone (IX) in trichlorobenzene; *p*, 4770 (4·00), 4550 (4·24); $\beta$ 3400 (4·60).
(– · – · – · –) 2:3,7:8-Dibenzoperinaphthenone in alcohol; *p*, 4000 (4·06), 3270 (4·02), 3030, (4·22); $\beta$, 2570 (4·58).

to experience.[5] The molecular weight of the hydrocarbon was estimated* by the mass spectroscopic method to be $510 \pm 5$ (Calc. 526). This shows that two rings have in fact been added to the dihydro hydrocarbon IV.

Confirmation that structure XI is correct, was obtained by comparison of the infrared spectra of the benzenoid hydrocarbons, given in Table 1. Groenwege[6] has shown that the $\gamma$-vibrations of the C—H bonds (735–900 $cm^{-1}$), can be used to establish the structure of polycyclic hydrocarbons. Recently Zander[7] applied this method to tetrabenzopentacene XII, the synthesis of which from two molecules of triphenylene in an aluminium chloride melt was not unambiguous. The Table shows that tetrabenzopentacene XII, as well as tetrabenzoheptacene XI, have "solo" C—H vibrations which are lacking in 1,2:6,7-dibenzopyrene XIV, which is also fully benzenoid.

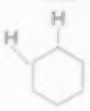
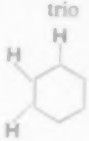
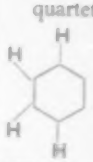
* The molecular weight was kindly measured by Dr. R. I. Reed of this department.

[5] E. Clar, *Ber. Dtsch. Chem. Ges.* **76**, 611 (1943); **81**, 520 (1948).
[6] M. P. Groenwege, *Colloquium Spectroscopicum Internationale VI Amsterdam* p. 579. Pergamon Press, London (1956).
[7] M. Zander, *Chem. Ber.* **92**, 2744 (1959).

Moreover, the resemblance of the infra-red spectra of tetrabenzoanthracene XIII, tetrabenzopentacene XII, and tetrabenzoheptacene XI is very striking.

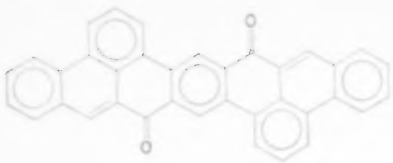
Further evidence that the hydrocarbon has structure XI is supplied by the comparison of the phosphorescence spectra of tetrabenzoanthracene XIII, tetrabenzopentacene XII, and tetrabenzoheptacene XI. The principal phosphorescence

TABLE 1. INFRA-RED SPECTRA

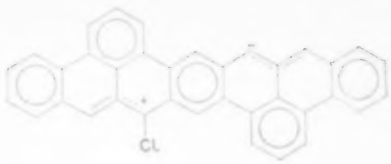
| Hydrocarbon | | C—H Vibrations ($cm^{-1}$)* | | | |
|---|---|---|---|---|---|
| | | solo 900–860 $cm^{-1}$ | duo  860–800 $cm^{-1}$ | trio  810–750 $cm^{-1}$ | quartet  770–735 $cm^{-1}$ |
| | XIV | — | — | 801 | 744 |
|  | XIII | 870 | — | — | 749 |
| | XII | 871<br>863 | — | 795 | 746 |
|  | XI | 867 | — | 792 | 745 |

* All spectra in KBr

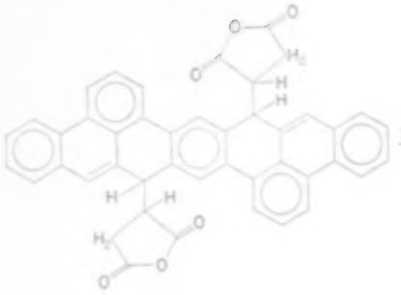
maxima are given in Table 2. The differences between the first phosphorescence bands of these hydrocarbons are so small (235 Å and 115 Å respectively), that they can result only from the annellation of fully benzenoid rings, for which such minimum shifts are typical. Contrary to this, the differences of phosphorescence bands in the acene series where there is only one benzenoid ring are the largest recorded and are



IX

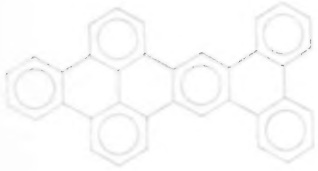


VIII

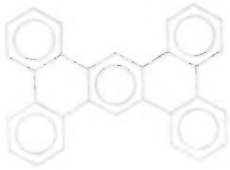


X

XI



XII



XIII

in the order of thousands of Ångstroms. Other series of hydrocarbons show shifts of intermediate magnitude.[6]

## EXPERIMENTAL*

### 1,4-*Di*-(*octahydrophenanthroyl*-9)-*benzene* I

Finely powdered terephthalyl chloride (75 g) was mixed with excess of technical octahydrophenanthrene (405 g), and benzene (500 ml). Powdered aluminium chloride (130 g) was added in portions. When the vigorous evolution of hydrochloric acid had ceased, the mixture was decomposed with ice and dil hydrochloric acid. The crude ketone was filtered off, dissolved in xylene, and combined with the benzene mother liquor. This mixture was washed very thoroughly with hot water and dil ammonia. Removal of the xylene–benzene mixture left the crude ketone (200 g), which was used directly for the pyrolysis. Repeated crystallization of a portion of ketone from xylene gave small, pale yellow needles m.p. 201–202°. The solution in conc sulphuric acid was brown at first, later turning orange. (Found: C, 85·9; H, 7·5. $C_{36}H_{34}O_2$ requires: C, 86·0; H, 7·6%).

### *Pyrolyses of* 1,4-*di*-(*octahydrophenanthroyl*-9)-*benzene* I

The crude ketone (100 g) was melted and the temp raised gradually to 400°; water was evolved and the brownish colour lightened to pale orange with a strong yellow fluorescence. When no more water appeared (½–¾ hr), heating was stopped and the mixture was cooled, with the exclusion of air.

* Melting points are uncorrected and were taken in evacuated capillaries. Microanalyses by Mr. J. M. L. Cameron and his staff of this department.

[6] E. Clar and M. Zander, *Chem. Ber.* **89**, 749 (1956).

TABLE 2. PHOSPHORESCENCE SPECTRA*

| Hydrocarbon | Phosphorescence maxima (A) |
|---|---|
| XIII | 4865 (weak, 5300 (strong), 5730 (medium) |
| XII | 5100 (medium), 5545 (strong), 5990 (weak) |
|  XI | 5215 (strong), 5685 (strong), 5930 (weak) |

* In solid ethanolic solution at 77IK.

Hot xylene (150 ml) was added and on cooling a red solid (5 g) was deposited. Further portions (2–3 g) were later obtained from the mother liquor. This crystalline pyrolysate consisted of a mixture of hydrogenated hydrocarbons, mainly the dihydro IV, with some octahydro III and a trace of the fully aromatic dibenzoheptazethrene VI. This crystalline mixture was used directly for subsequent reactions. The mixture dissolved slowly in conc sulphuric acid and gave a violet colour at first which changed to purple.

*Tetradecahydro*-4,5:12,13-*dibenzoheptazethrene* II

The filtrate from the above reaction was chromatographed on alumina. Elution with petroleum ether (60–80°) and then benzene, gave several fractions. The major portion was a viscous oil which could not be characterized. Later fractions gave a small amount (50 mg) of a yellow crystalline hydrocarbon m.p. 438–440° which gave yellow solutions in conc sulphuric acid. (Found: C, 92·1; H, 7·5. $C_{26}H_{34}$ requires: C, 92·6; H, 7·4%).

1,3-*di*-(*octahydrophenanthroyl*-9)-*benzene* V

Procedure as for ketone I. Crystallization from benzene and petroleum ether (100–120°) gave white needles m.p. 172–173° which dissolved in conc sulphuric acid to give a brown solution which later turned orange. (Found: C, 86·0; H, 7·9. $C_{26}H_{34}O_2$ requires: C, 86·0; H, 7·6%).

*Pyrolyses of* 1,3-*di*-(*octahydrophenanthroyl*-9)-*benzene* V

Conditions were the same as for ketone I. The crude ketone (100 g) gave the mixed hydrogenated hydrocarbons (6 g).

4,5:12,13-*Dibenzoheptazethrene* VI

(i) *Dehydrogenation with palladium charcoal.* The crystalline pyrolysate (500 mg) was sublimed, in a current of air free carbon dioxide, over 15% palladium charcoal at 300–320°/0·1 mm. Shining green needles (450 mg) of the fully aromatic hydrocarbon VI were formed, dec pt above 400°. Solutions of the hydrocarbon VI in organic solvents were violet-red with a strong red fluorescence. The dibenzo heptazethrene VI dissolved immediately in conc sulphuric acid to give a deep purple solution which showed absorption bands in the visible region at 550 mμ, and 512 mμ. (Found: C, 95·2; H, 4·7. $C_{26}H_{20}$ requires C, 95·55; H, 4·46%).

(ii) *Dehydrogenation with nitrobenzene.* The pyrolysate (1 g) was suspended in nitrobenzene (15 ml), and refluxed for 2–3 min. The brownish red solution turned deep purple with a strong red fluorescence and on cooling glistening green needles (300 mg) were deposited.

(iii) *Dehydrogenation using chloranil in trichlorobenzene.* The pyrolysate (1 g) was suspended in trichlorobenzene (20 ml) and excess chloranil (1 g) added. The mixture was boiled for 2–3 min and on cooling crystals (200 mg) of the hydrocarbon XI were formed.

*Salts of* 4,5:12,13-*dibenzoheptazethrene* VII

(i) *Hydrochloride.* Solutions of the hydrocarbon VI in trichlorobenzene were shaken with conc hydrochloric acid. The organic layer was completely decolourized and a violet salt formed. The salt could also be formed by the passage of hydrochloric acid gas. A solution of hydrocarbon VI (100 mg) in trichlorobenzene (500 ml), was saturated with hydrochloric acid gas. The flocculant violet precipitate was filtered off, washed with dry benzene, and dried *in vacuo*. (Found: C, 88·0; H, 4·3; Cl, 6·8. $C_{36}H_{21}Cl$ requires: C, 88·4; H, 4·3; Cl, 7·3%).

The hydrochloride decomposed on standing, turning black, with loss of hydrochloric acid. If a suspension of the salt in trichlorobenzene was allowed to stand for several days a solution with the absorption bands (600, 500m$\mu$) of the chlorodibenzozethrene VIII resulted. The hydrochloride appeared insoluble in most organic solvents. When a suspension of the salt in pyridine was boiled green crystals of the parent hydrocarbon VI were formed. The salt gave purple solutions in conc sulphuric acid which had bands at 550 m$\mu$ and 512 m$\mu$.

(ii) *Sulphate.* Solutions of dibenzoheptazethrene VI were completely decolourized on shaking with 80% sulphuric acid. The violet sulphate being formed. Dibenzoheptazethrene VI gave solutions in conc sulphuric acid which showed absorption bands at 550 m$\mu$, and 512 m$\mu$, compared to the hydrocarbon VI in trichlorobenzene solution where the bands were at 572 m$\mu$ and 528 m$\mu$. This shift is indicative of salt formation.

(iii) *Perchlorate and phosphate.* Solutions of dibenzoheptazethrene in trichlorobenzene were also decolourized when shaken with perchloric or phosphoric acid, the violet salts being precipitated.

7-*Chloro*-4,5-*dibenzoheptazethrene* VIII

An excess of phosphorus pentachloride (500 mg) was added to a suspension of the crystalline pyrolysate (300 mg) in boiling xylene. The reddish-brown solution turned a deep blue with a strong red fluorescence and on cooling the dark blue chlorohydrocarbon VIII (250 mg) was deposited. Recrystallization from trichlorobenzene gave the pure chlorohydrocarbon, dec pt above 450°, which dissolved in conc sulphuric acid to give a deep purple solution. (Found: Cl, 7·3. $C_{36}H_{19}Cl$ requires: Cl, 7·5%).

7,15-*Dihydro*-4,5:12,13-*dibenzoheptazethrene* IV

Although this substance is the main product of the pyrolysis the best method of obtaining it pure was by reduction of dibenzoheptazethrene VI, or chlorodibenzheptazethrene VIII. Dibenzoheptazethrene VI (500 mgs) or chlorodibenzheptazethrene VIII (500 mgs), was ground together with zinc dust (2 g). This mixture was suspended in pyridine (100 ml) and refluxed. Acetic acid (80%, 10 ml) was added slowly over 3 hr. The violet solution, decolourized immediately becoming a pale yellow with a strong blue fluorescence. After cooling the solution was filtered into water and boiled. The pale yellow dihydro-dibenzoheptazethrene was filtered off, dried and sublimed, m.p. 395–400° (dec). The colour in conc sulphuric acid was violet. (Found: C, 94·6; H, 5·4. $C_{36}H_{22}$ requires: C, 95·1; H, 4·9%). This hydrocarbon could not be recrystallized since it was too easily dehydrogenated.

4,5:12,13-*Dibenzoheptazethrene*-7,15-*quinone* IX

The crystalline pyrolysate (300 mg) and selenium dioxide (100 mg) were refluxed in nitrobenzene (10 ml) for 20 min. The red solution turned purple and then dark brown. On cooling the product was filtered off, washed with nitrobenzene and methanol, followed by hot water to remove excess selenium dioxide. The dark brown product (400 mg) was purified by sublimation. Brown needles of the quinone (200 mg) sublimed at 400°/0·1 mm, dec pt. above 450°. The colour in conc sulphuric acid was green. (Found: C, 89·5; H, 4·3. $C_{36}H_{18}O_2$ requires: C, 89·6; H, 3·8%).

*Maleic anhydride adduct* X *from 7,15-dihydro-4,5-dibenzoheptazethrene* IV

The pyrolysate (5 g) was added to molten maleic anhydride and boiled for 15 min. After cooling, the mixture was poured into water and digested. The crude light brown anhydride X was filtered off, and dissolved in 15–20% caustic potash solution, giving a pale yellow colour with blue fluorescence. Zinc dust was added to prevent aerial oxidation and after filtration the solution was acidified. The brown acid was dried (6·5 g). A portion was crystallized from acetic anhydride, m.p. 250–255° (dec). (Found: C, 78·8; H, 4·8. $C_{44}H_{28}O_7$; (semi-anhydride) requires: C, 79·0; H, 4·3). The solution in conc sulphuric acid was steel blue at first, later turning reddish.

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*Octahydro*-4,5:12,13-*dibenzoheptazethrene* III

When the above condensation was carried out for a shorter time there was an alkali insoluble residue (200 mg). Recrystallization from benzene gave small white needles, m.p. 318–320°. This hydrocarbon III could not be dehydrogenated by means of chloranil in trichlorobenzene, but sublimation over 15% palladium charcoal at 300–320° gave a dibenzoheptazethrene VI in quantitative yield. The octahydro hydrocarbon III gave a blue solution in conc sulphuric acid. (Found: C, 93·5; H, 6·3. $C_{28}H_{28}$ requires; C, 93·9: H, 6·1%).

5,6:8,9:14,15:17,18-*Tetrabenzoheptacene* XI

The tetracarboxylic acid, derived from X, (5 g) was ground together with zinc dust (5 g). Zinc chloride (50 g), sodium chloride (5 g) and a little water (2 ml) were added and the temp of the mixture was raised, with constant stirring, to 300–320° for 10 min. After cooling the mixture was digested with dil acetic acid and the zinc dust dissolved in dil hydrochloric acid. The crude product (2 g) was extracted with ether and xylene, to remove impurities of low molecular weight. Repeated sublimation (400–450°/0·1 mm), followed by recrystallization from methyl naphthalene gave yellow needles (300 mg) of tetrabenzoheptacene, m.p. 480–490° (sublim). Tetrabenzoheptacene does not dissolve in conc sulphuric acid although the surface of the crystals turns black. The hydrocarbon has a long life phosphorescence in solid ethanolic solution at 77 K°. (Found: C, 95·5; H, 4·5. $C_{42}H_{22}$ requires: C, 95·8; H, 4·2%). The molecular weight was found to be 510 ± 5, $C_{42}H_{22}$ requires 526.

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# DYES CONTAINING THE INDOLE RING—I

## TRINUCLEAR PENTAMETHINCYANINES

J. R. MAJER
The Chemistry Department, The University of Birmingham

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**Abstract**—Indole trimethincyanines prepared as described previously[1] and also by the interaction of indoles containing unsubstituted NH- and β-positions with acetylenic aldehyde acetals have been found to condense with homocyclic and heterocyclic aldehydes to yield trinuclear dyes. A simple method of preparing unsymmetrical trimethincyanines is described.

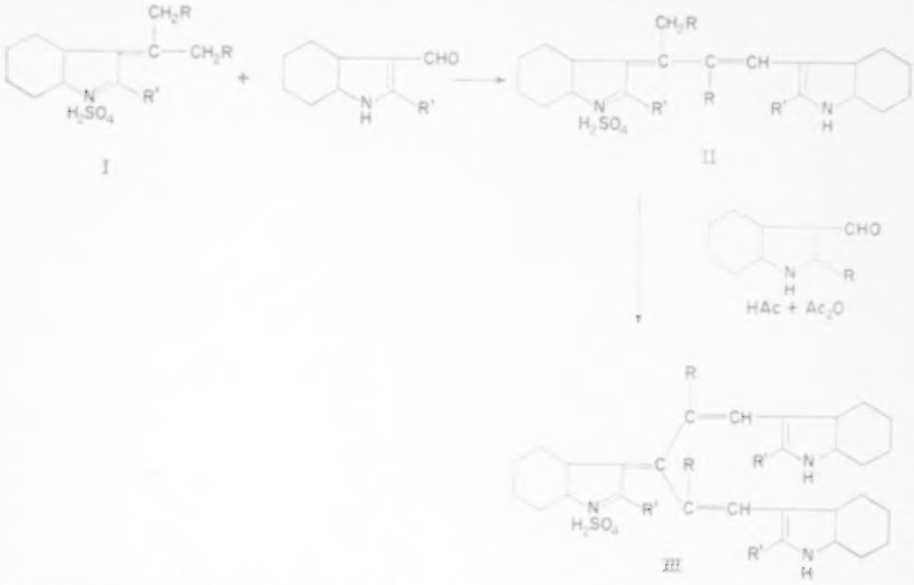
IT was shown in a previous paper that indoles containing unsubstituted NH- and β-positions react with a large excess of a carbonyl compound and a molecular equivalent of concentrated sulphuric acid to yield yellow crystalline salts having the structure I (R = hydrocarbon residue, R′ = H or a hydrocarbon residue). When the carbonyl compound contains the group —CO·$CH_2$— the products, such as 2-methyl-3-isopropylidene indolenine sulphate, condense with homocyclic and heterocyclic aldehydes to yield trimethincyanines II. Because the two methyl groups in the isopropylidene groups are essentially equivalent, it seemed probable that the trimethincyanine II should be capable of further reaction with a second molecule of aldehyde to yield the trinuclear dye III. When, however, I was refluxed in acetic acid with an excess of 2-methyl-3-indole aldehyde for a prolonged period, only the purple trimethincyanine II was obtained.

It is concluded that when the first methyl group has reacted and the trimethincyanine has been formed, the reactivity of the remaining methyl group is reduced, possibly owing to steric effects. Bis-(2-methyl-3-indole)-α-methyl trimethincyanine sulphate was therefore refluxed with 2-methylindole-3-aldehyde in a 1 : 1 mixture of acetic anhydride and glacial acetic acid. The original purple colour of the solution was rapidly replaced by a deep blue colour and green crystals were deposited. These were shown by analysis to be the expected trinuclear dye III. A similar dye was obtained when the aldehyde used was Fischer's base aldehyde.

Because of the tedious nature of the preparation of indole-3-aldehydes, alternative routes to the trimethincyanines were investigated. König[2] described the use of propargyl aldehyde diethyl acetal in the preparation of indole and pyrrole trimethincyanines and his method was extended to the substituted acetylenic acetals. An alternative route employing acetylenic ketones has been described by Johnson.[3] Crotonaldehyde was brominated and the resulting dibromide acetalized with ethyl orthoformate. Debromination with alcoholic caustic potash gave α-methyl propargyl aldehyde diethyl acetal. This compound reacted readily in glacial acetic acid solution with both

[1] A. H. Cook and J. R. Majer, *J. Chem. Soc.* 486 (1944).
[2] W. König, *Angew. Chem.* 38, 743 (1925).
[3] A. W. Johnson, *J. Chem. Soc.* 1626 (1947).

pyrroles and indoles in the presence of mineral acid to yield trimethincyanines. α-Phenol propargyl aldehyde diethyl acetal was prepared similarly from cinnamaldehyde.[4] Crystalline trimethincyanines were obtained from propargyl aldehyde diethyl acetal with 2,4-diphenylpyrrole, and 2-methyl-3-carbethoxy-4-phenylpyrrole-α-methyl propargyl aldehyde diethyl acetal with 2-phenyl-4-*o*-chlorophenylpyrrole,



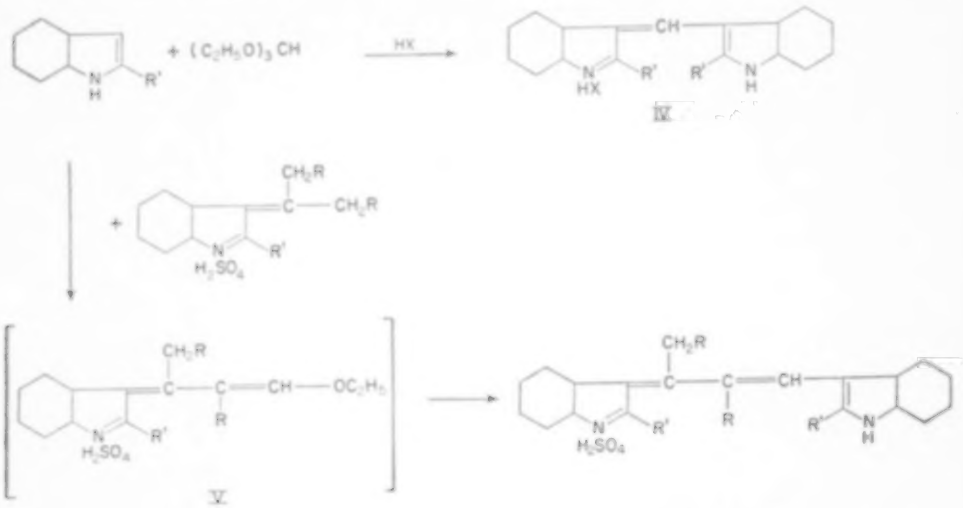

2-methyl-3-carbethoxy-4-phenylpyrrole, 2,4-diphenylpyrrole, 2-methylindole and 2-phenylindole, and α-phenyl propargyl aldehyde diethyl acetal with 2-phenyl-4-*p*-anisylpyrrole, 2,4-diphenylpyrrole, 2-methyl-4-phenylpyrrole and 2-methyl-3-carbethoxy-4-phenylpyrrole. In each case the dye obtained was identical with that prepared by the original method. In the case of pyrrole itself only an insoluble amorphous precipitate was obtained when mineral acid was added to a solution in the presence of an acetylenic acetal although there was an initial development of the expected purple colour. This is believed to be due to the rapid resinification of the pyrrole by the acid. Attempts to prepare dyes from N-substituted pyrroles were equally unsuccessful; when an acetic acid solution of 1,2-dimethyl-3-carbethoxy-4-phenylpyrrole was treated with mineral acid in the presence of an acetylenic acetal a deep blue colour developed but there was no precipitate. Addition of water or ether decolourized the solution and deposited a whitish solid. On standing in glacial acetic acid solution the colour slowly faded. Similar fugitive colours were obtained with α-substituted β-free pyrroles such as 2,5-dimethyl-, 2,5-dimethyl-1-cyclohexyl- and 2,5-dimethyl-1-stearyl-pyrroles.

Attempts were made to condense the pyrrole trimethincyanines prepared from α-methyl propargyl aldehyde diethyl acetal with aldehydes, but on prolonged refluxing in the acetic acid–acetic anhydride mixture the original blue colour of the trimethincyanine gradually faded without the appearance of any deposit. It is concluded that the

[4] *Org. Synth.* **25**, 92.

trinuclear dyes derived from pyrrole are unstable. Bis-3-(2-phenyl indole)-α-methyl trimethincyanine sulphate, however, reacted readily with 2-methylindole-3-aldehyde although the resulting trinuclear dye was so insoluble that it was precipitated without imparting any colour to the refluxing solution.

Unsymmetrical indole trimethincyanines were prepared by the addition of a hot solution of an indole in ethyl orthoformate to a boiling solution of I in glacial acetic acid, thus avoiding the use of the indole-3-aldehydes. The exact course of this reaction is not clear:—β-free indoles do not react with boiling ethyl orthoformate and on



addition of mineral acid the di-indolyl methene IV is formed. The same product is obtained even if a ketone such as acetone is present, so that the most rapid reaction must be the formation of the methene. This is not the case with pyrroles, where in the presence of ketones, trimethincyanines are formed.[1] The most plausible explanation is that the indolenine salt I reacts with the ortho ester to form V which then condenses with the indole to produce the trimethincyanine. Attempts to isolate V have been unsuccessful.

Unsymmetrical trimethincyanines were prepared by the condensation of 2-methyl-3-isopropylidene indolenine sulphate with ethyl orthoformate and indole, 2,4-diphenylpyrrole and 2-phenylindole; 2-phenyl-3-isopropylidene indolenine sulphate was condensed with ethyl orthoformate and indole. The unsymmetrical trimethincyanines were converted to the trinuclear dyes by refluxing with aldehydes in glacial acetic acid–acetic anhydride mixture. Indole-3-aldehyde was condensed with 3-(2-methylindole)-3-indole-α-methyl trimethincyanine sulphate and with 3-(2-methylindole)-3-(2-phenylindole)-α-methyl trimethincyanine sulphate. In the latter case the product contained three different nuclei connected by a chain of five carbon atoms. In order to simplify the nomenclature of these trinuclear dyes they are treated as derivatives of indole pentamethincyanines although their nearest relatives in the true cyanines are the trinuclear neocyanines.[5]

[4] F. M. Hamer, R. J. Rathbone and B. S. Winton, *J. Chem. Soc.* 1434 (1947); 1872 (1948).

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## EXPERIMENTAL

*Symmetrical trimethincyanines*

2-Diphenylpyrrole (2·19 g) and propargyl aldehyde diethyl acetal (0·6 g) were refluxed in glacial acetic acid (10 ml) and 50% hydrobromic acid in glacial acetic acid (0·81 ml) added. A deep blue colour appeared and green crystals were precipitated. On crystallization from chloroform bis-2-(3,5-diphenylpyrrole) trimethincyanine bromide (1·1 g) was obtained as bronze octahedra m.p. 260°. (Found: Br, 14·35%; $C_{35}N_{29}N_2Br$ requires: Br, 14·35%).

2-Methyl-3-carbethoxy-4-phenylpyrrole (2·3 g) gave bis-2-(3-phenyl-4-carbethoxy-5-methylpyrrole) trimethincyanine bromide as green rods from formic acid m.p. 200°.

2-Phenyl-4-*o*-chlorophenylpyrrole (2·53 g) and methyl propargyl aldehyde diethyl acetal (1·02 g) gave bis-2-(3-*o*-chlorophenyl-5-phenylpyrrole)-α-methyl-trimethincyanine bromide (0·9 g) as black needles from glacial acetic acid m.p. 158°. (Found: Br, 12·2%; $C_{41}H_{29}N_2Cl_2Br$ requires: Br, 12·5%).

2-Methyl-3-carbethoxy-2-phenyl pyrrole (2·3 g) gave bis-2-(3-phenyl-4-carbethoxy-5-methylpyrrole)-α-methyl-trimethincyanine bromide as matted green needles from formic acid m.p. 198°.

2-Methylindole (1·3 g) and methyl propargyl aldehyde diethyl acetal (0·71 g) and sulphuric acid (0·28 ml) gave bis-3-(2-methylindole)-α-methyl-trimethincyanine sulphate as long green needles from glacial acetic acid m.p. 168°.

2-Phenylindole (7·7 g) gave bis-3-(2-phenylindole)-α-methyl-trimethincyanine sulphate (6·2 g) as copper crystals from acetic acid–ether m.p. 178°. (Found: S, 5·9%; $C_{53}H_{36}O_4N_2S$ requires: S, 5·99%).

2-Phenyl-4-*p*-anisylpyrrole (2·49 g), phenyl propargyl aldehyde diethyl acetal (1·02 g) and 50% hydrobromic acid gave bis-2-(3-*p*-anisyl-5-phenylpyrrole)-α-phenyl-trimethincyanine bromide as dark green crystals from glacial acetic acid m.p. 240°. (Found: Br, 11·7%; $C_{43}H_{35}O_2N_2$ Br requires: Br, 11·55%).

2-Methyl-3-carbethoxy-4-phenylpyrrole gave bis-2-(3-phenyl-4-carbethoxy-5-phenylpyrrole)-α-phenyl-trimethincyanine bromide as green needles from ethyl formate m.p. 202°.

2,4-Diphenylpyrrole gave bis-2-(3,5-diphenylpyrrole)-α-phenyl-trimethincyanine bromide as brassy crystals from chloroform m.p. 247°.

*Unsymmetrical trimethincyanines*

2-Methyl-3-isopropylidene indolenine sulphate (5·86 g) was dissolved in glacial acetic acid (20 ml) and the mixture heated to boiling. A boiling solution of indole (2·3 g) in ethyl orthoformate (3 ml) was added when a vigorous reaction occurred and the solution became deep red. On cooling and dilution with ether an oil was precipitated which hardened to a brown solid when ground with water. Crystallization from acetic acid–ether yielded 3-(2-methylindole(-3′-indole-α-methyl-trimethincyanine sulphate (6·2 g) as brown metallic needles m.p. 172°. (Found: S, 8·0%; $C_{21}H_{20}O_4N_2S$ requires: S, 8·08%).

2-Phenylindole (3·86 g) gave 3-(2-methylindole)-3′-(2-phenylindole)-α-methyl-trimethincyanine sulphate (6·4 g) as purple brown needles m.p. 106°. (Found: S, 6·6%; $C_{27}H_{24}O_4N_2S$ requires: S, 6·78%).

2,4-Diphenylpyrrole (2·2 g) gave 3-(2-methylindole)-2′-(3,5-diphenylpyrrole)-α-methyl-trimethincyanine sulphate (0·6 g) as copper octahedra from chloroform–ether m.p. 136°. (Found: S, 6·3%; $C_{29}H_{26}O_4N_2S$ requires: S, 6·42%).

2-Phenylindole (3·86 g) was dissolved in acetone (5 ml) and A.R. conc sulphuric acid (1·1 ml) added. The excess acetone was removed under reduced pressure and the residue dissolved in glacial acetic acid (20 ml). The solution was refluxed and a boiling solution of indole (2·3 g) in ethyl orthoformate (3 ml) added. After refluxing for 5 min the red dye was precipitated by addition of ether and the resulting oil ground with water. On crystallization from acetic acid–ether 3-(2-phenylindole)-3′-indole-α-methyl-trimethincyanine sulphate was obtained as purple needles m.p. 174°. (Found: S, 6·98%; $C_{35}H_{28}O_4N_2S$ requires: S, 6·99%).

*Trinuclear dyes*

Indole-3-aldehyde (1·0 g) and 3-(2-methylindole)-3′-(2-phenylindole)-α-methyl-trimethincyanine sulphate (3·6 g) were refluxed for 2 min in a 1 : 1 mixture of acetic acid and acetic anhydride (20 ml).

The solution became an intense brown colour and deposited a black solid. On crystallization from methanol, 3-(2-phenylindole)-3′-indole-γ-3″-(2-methylindole) pentamethincyanine sulphate (3 g) was obtained as black metallic needles m.p. 143°. (Found: S, 5·3%; $C_{35}H_{29}O_4N_3S$ requires: S, 5·34%).

Indole-3-aldehyde (1·0 g) and 3-(2-methylindole)-3′-indole α-methyl-trimethincyanine sulphate (3·3 g) gave bis-3-(indole)-γ-3-(2-methylindole) pentamethincyanine sulphate (2·3 g) as black metallic needles from methanol m.p. 120°. (Found: S, 6·0% N, 8·0%; $C_{30}H_{25}O_4N_3S$ requires: S, 6·12%, N, 8·03%). Treatment with ammonia solution gave the free base as a brown solid m.p. 2480°. (Found: N, 10·0%; $C_{30}H_{23}N_3$ requires: N, 9·08%).

2-Methyl-3-indole aldehyde (0·74 g) and bis-(2-phenylindole)-α-methyl-trimethincyanine sulphate (2·6 g) gave (2-phenylindole)-3′-(2-methylindole)-γ-3″-(2-phenylindole) pentamethincyanine sulphate (2·0 g) as black metallic needles from methanol m.p. 310°. (Found: S, 4·4%, N, 6·2%; $C_{42}H_{33}O_4N_3S$ requires: S, 4·74%, N, 6·34%).

Bis-3-(2-methylindole)-α-methyl-trimethincyanine sulphate (0·6 g) and Fischer's base aldehyde (0·3 g) gave 3-(2-methylindole)-2′-(1,3,3′-trimethylindolenine)-γ-3″-(2-methylindole) hexamethincyanine sulphate (0·5 g) as copper octahedra from acetic acid–ether m.p. 184°. (Found: S, 5·25%, N, 7·0%; $C_{35}H_{33}O_4N_3S$ requires: S, 5·4%, N, 7·08%).

2-Methyl-3-indole aldehyde (0·4 g) and bis-3-(2-methylindole)-α-methyl-trimethincyanine sulphate (1·02 g) gave bis-3-(2-methylindole)-γ-3′-2-methylindole) pentamethincyanine sulphate (0·86 g) as small green needles from acetic acid m.p. 281°. (Found: S, 5·7%, 7·5%; $C_{32}H_{29}O_4N_3S$ requires: S, 5·81%, N, 7·62%).

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# DYES CONTAINING THE INDOLE RING—II
## TRINUCLEAR TRIMETHINCYANINES

J. R. MAJER
The Chemistry Department, The University of Birmingham

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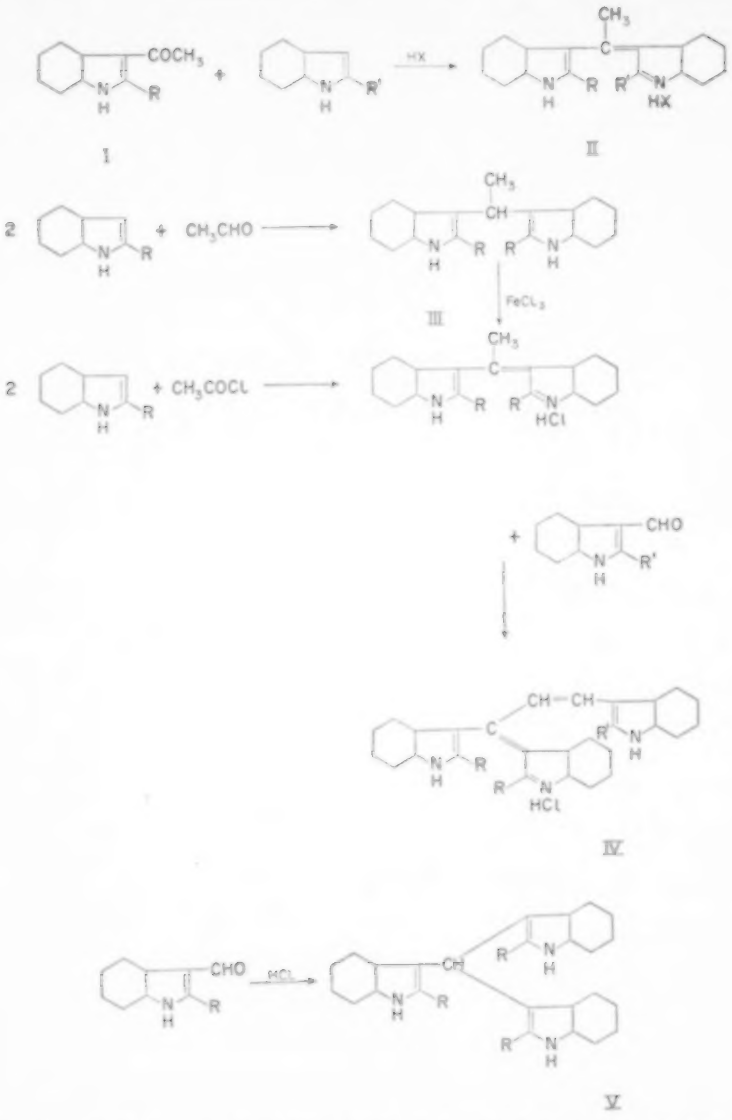
**Abstract**—Representative indoles containing a free β-position have been condensed with aliphatic acid chlorides or acid anhydrides and the products identified as substituted di-indolylmethenes. A substituted unsymmetrical di-indolylmethene has been synthesized by the condensation of 2-methyl-3-acetylindole with 2-phenylindole in the presence of phosphorus oxychloride. Some of these methenes have been shown to contain a reactive methylene group and have been condensed with both homocyclic and heterocyclic aldehydes to yield intensely coloured trinuclear dyes.

In view of the demonstration of the reactivity of the α-methyl group in α-methyl-trimethincyanines derived from the indole nucleus,[1] the possibility of preparing trinuclear indole trimethincyanines by the condensation of α-methyl-di-indolylmethenes (I) with heterocyclic aldehydes was investigated. Such di-indolylmethenes can be considered as cyanines but since the majority of them have already been described as methenes uniformity of nomenclature has been sacrificed in order to avoid confusion.

THE simplest route to α-methyl-di-indolylmethenes I appeared to be interaction of β-free indoles with 3-acetylindoles II. 2-Methylindole was refluxed with varying amounts of acetic anhydride and sodium acetate for periods up to 7 hr without noticeable conversion of the indole. In the search for a more vigorous reagent 2-methylindole was warmed with acetyl chloride. On raising the temperature of the mixture to 100°, a vigorous reaction occurred, there was a copious evolution of hydrogen chloride and the mixture became bright scarlet in colour. The dye was isolated by precipitation from glacial acetic acid solution with water, in the form of a brown solid soluble in polar solvents. The solutions faded to a yellow colour on addition of alkalies or ammonia but the original red colour was restored by the addition of acid. This behaviour resembled that of the di-indolylmethenes first named "Rosindoles" by Fischer.[2] The substituted di-indolylmethenes have been prepared by the oxidation of the analogous di-indolylmethanes (III) formed by the interaction of β-free indoles with aldehydes.[3] 2-Methylindole was condensed with acetaldehyde in alcohol solution to yield α,2,2′-trimethyl-di-indolylmethane. Upon oxidation with ferric chloride a red dye was produced identical with that formed by the interaction of 2-methylindole and acetyl chloride, which is identified as α,2,2′-trimethyl-di-indolylmethene hydrochloride. Since this constituted the desired intermediate it was refluxed with *p* dimethylaminobenzaldehyde in glacial acetic acid. The original red colour of the solution changed gradually to an intense blue and on addition of ether a black solid was precipitated having the characteristics of a dye of the "Ehrlich" type, being reversibly decolourized by both acids and alkalies. Other dyes were prepared from 2-methyl-3-carbethoxy-4-phenyl-5-pyrrole aldehyde and 2-methyl-3-indole aldehyde.

[1] Part 1: J. R. Majer, *Tetrahedron* **9**, 106 (1960).
[2] E. Fischer and P. Wagner, *Ber. Dtsch. Chem. Ges.* **20**, 815 (1887).
[3] M. Freund and G. Lebach, *Ber. Dtsch. Chem. Ges.* 36, 308 (1903).



Analysis showed all three to be trinuclear dyes formed by the elimination of water between the reactants. Despite the strong presumption that the reaction took place with the α-methyl group alone no direct evidence was available and therefore 2,2′-dimethyl-di-indolylmethene hydrochloride was prepared by the interaction of 2-methylindole, ethyl orthoformate and hydrochloric acid. It showed no reactivity whatever towards aldehydes. The trinuclear dye prepared by the reaction of 2-methyl-3-indole aldehyde and α,2,2′-trimethyl-di-indolylmethene hydrochloride (IV) has a certain formal resemblance to that prepared by Ellinger[4] from 2-methylindole and 2-methyl-3-indole aldehyde (V). Propionyl chloride and phenacetyl chloride were not

[4] A. Ellinger, H., 1911, 71, 13.

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as reactive as acetyl chloride and substantial yields were only obtained by prolonged refluxing in glacial acetic acid. Succinyl chloride on the other hand was more reactive and the condensation proceeded so vigorously that small particles of dye were carried up with the evolved hydrogen chloride which became tinged pink.

2-Phenylindole was less reactive than 2-methylindole and was refluxed for several hours with acetyl chloride in glacial acetic acid solution before reaction was complete.

α-Methyl-di-indolylmethene hydrochloride proved surprisingly difficult to synthesize; indole reacted vigorously at room temperature with acetyl chloride but the product was a pink glass which showed no further sign of reactivity and was probably polymeric in nature. Diluents such as acetic acid or acetic anhydride moderated the reaction but only unreactive tars were produced. König[5] has described the preparation of di-indolylmethenes by the interaction of indoles and ethyl orthoformate in ethanol solution in the presence of perchloric acid, but no crystalline products were isolated when ethyl orthoacetate was substituted or the perchloric acid replaced by other mineral acids. The methene was finally prepared by adding hydrobromic acid to a boiling solution of indole in acetic anhydride; it was precipitated from the resulting orange solution as a brown solid by the addition of ether. It was less reactive than any of the other methenes and the only trinuclear dye which could be isolated was prepared by heating it with *p* dimethylaminobenzaldehyde in acetic anhydride solution. There was a surprising variation in stability in the trinuclear dyes derived from *p* dimethylaminobenzaldehyde and the methenes. Those prepared from α-ethyl and α-benzyl 2,2′-dimethyl-di-indolylmethenes were rapidly destroyed in hot acetic anhydride, while those derived from α,2,2′-trimethyl-indolyl and α,α′-ethylene-bis-3-(2,2′-dimethyl-di-indolylmethene hydrochloride) were quite stable. When dyes were prepared from indole aldehydes as in the case of that obtained from 2-methyl-3-indole aldehyde and α-methyl-2,2′-diphenyl-di-indolylmethene hydrochloride it was important to free the methene from traces of uncombined hydrogen chloride for it has been shown that indole-3-aldehydes react in the presence of mineral acids to form the di-indolylmethenes (formerly called "uroroseins") by the elimination of formic acid.[6]

The synthesis of unsymmetrical di-indolylmethenes could only be achieved by the interaction of indole-3-methyl ketones and indoles unsubstituted in the 3-position. 2-Methyl-3-acetyl indole was prepared by the method of Salway.[7] A 30 per cent yield of 2-methyl-3-acetyl indole was obtained by treating 2-methylindole magnesium bromide with acetyl chloride in ether. The ketone was very unreactive and did not form methenes with indoles by treatment with mineral acids in acetic acid–acetic anhydride mixture. It condensed with 2-phenylindole in phosphorus oxychloride solution from which it was isolated as a red powder. The resulting unsymmetrical methene reacted readily in hot acetic acid–acetic anhydride mixture to yield trinuclear dyes with *p*-dimethylaminobenzaldehyde and 2-methyl-3-indole aldehyde.

## EXPERIMENTAL

*Di-indolylmethenes*

2-Methylindole (2·6 g) and ethyl orthoformate (1·6 g) were dissolved in hot glacial acetic acid (10 ml) and 50% hydrobromic acid in glacial acetic acid (1·6 ml) added. A vigorous reaction took

[5] W. König, *J. Prakt. Chem.* **84**, 217 (1911).
[6] J. Harley-Mason and J. D. Bu'lock, *Biochem. J.* **51**, 430 (1952).
[7] A. H. Salway, *J. Chem. Soc.* 384 (1913).

place and the solution became bright orange. After 3 min the solution was cooled and diluted with water to precipitate the 2,2′-dimethyl-di-indolylmethene hydrobromide as a brown solid. On crystallization from methanol it was obtained as brown needles m.p. 236°.

A solution of indole (3·3 g) in acetic anhydride (5 ml) was boiled and hydrobromic acid (50%) in glacial acetic acid (1·6 ml) added dropwise. On cooling α-methyl-di-indolylmethene hydrobromide (2·1 g) was precipitated as a brown powder by addition of ether. It was obtained from acetic acid–ether as a brown powder m.p. 153° (Found: C, 63·5, H, 4·5, Br, 23·3; $C_{18}H_{15}N_2Br$ requires: C, 63·65, H, 4·42, Br, 23·6%).

2-Methylindole (13 g) and acetyl chloride (3·7 ml) were heated at 100° for 4 hr and the mixture poured into water. The precipitated solid was crystallized from acetic acid–ether to yield α,2,2′-trimethyl-di-indolylmethene hydrochloride (13 g) as a brown powder m.p. 118° (Found: C, 74·2, H, 5·8, Cl, 11·0; $C_{20}H_{19}N_2Cl$ requires: C, 74·3, H, 5·88, Cl, 11·0%).

2-Methylindole (10 g) paraldehyde (5 g) and zinc chloride (1·0 g) were heated at 100° for 3 hr. The product was crystallized from ethanol to yield α,2,2′-trimethyl-di-indolylmethane (5·0 g) as colourless prisms m.p. 191°.

*Oxidation.* The methane (5 g) was dissolved in hot glacial acetic acid (20 ml) and ferric chloride (2·0 g) added. After refluxing for 10 min the bright red solution was diluted with hydrochloric acid and the precipitated solid ground with ammonia and crystallized from benzene to yield α,2,2′-trimethyl -di-indolylmethene as light brown needles m.p. 202° (Angeli and Marchetti R.A.L. (5) 16, II, 794 give m.p. 203°). The methene was dissolved in dry benzene and dry hydrogen chloride passed through the solution. The solid precipitated was crystallized from acetic acid–ether to yield α,2,2′-trimethyl-di-indolylmethene hydrochloride as a brown powder m.p. 119°.

2-Methylindole (13 g) and succinyl chloride (4 ml) were heated at 100° for 3 hr. The red tarry residue was treated with acetone and water and crystallized from acetic acid–ether to yield α,α′-ethylene-bis-3-(2,2′-dimethyl-di-indolylmethene hydrochloride) (12 g) as a light red powder m.p. 106° (Found: C, 74·6, H, 5·4, Cl, 11·2; $C_{40}H_{36}N_4Cl_2$ requires: C, 74·65, H, 5·6, Cl, 11·05%).

2-Methylindole (13 g) and propionyl chloride (4.6 g) were heated at 100° for 7 hr, dissolved in glacial acetic acid (50 ml) and refluxed for 4 hr. Addition of ether precipitated a black oil which solidified on grinding with water. Crystallization from acetic acid–ether gave α-ethyl-2,2′-dimethyl-methene hydrochloride as a black powder (15·3 g) m.p. 134° (Found: C, 75·0, H, 6·3, Cl, 10·4; $C_{21}H_{21}N_2Cl$ requires: C, 74·77, H, 6·23, Cl, 10·55%).

2-Methylindole (13 g) and phenacetyl chloride (7·7 g) were heated at 100° for 7 hr, dissolved in glacial acetic acid and refluxed for 4 hr. Addition of water precipitated a red oil which solidified on treatment with acetone and ether. Repeated crystallization from acetone–ether gave α-benzyl-2 2′-dimethyl-di-indolylmethene hydrochloride (6·2 g) as a brown powder m.p. 150° (Found: C, 78·1, H, 5·6, Cl, 9·0; $C_{26}H_{23}N_2Cl$ requires: C, 78·2, H, 5·76, Cl, 8·91%).

2-Phenylindole (4 g) and acetyl chloride (1 ml) were refluxed in glacial acetic acid (15 ml) for 4 hr and diluted with ether. The precipitate was repeatedly recrystallized from acetic acid–ether to yield α-methyl-2,2′-diphenyl-di-indolylmethene hydrochloride (4·2 g) as a black powder m.p. 192° (Found: Cl, 7·8, $C_{30}H_{23}N_2Cl$ requires: Cl, 7·95%).

2-Methyl-3-acetyl indole (3·66 g) and 2-phenylindole (3·86 g) were added in portions to phosphorus oxychloride (10 ml). The mixture became hot, evolving hydrogen chloride and assuming a cherry red colour. The mixture was left for 24 hr and poured onto cracked ice. The precipitate was crystallized from acetic acid–ether to yield α,2-dimethyl-2′-phenyl-di-indolylmethene hydrochloride (7 g) as pinkish needles m.p. 112° (Found: C, 77·8, H, 5·3, Cl, 9·1; $C_{25}H_{21}N_2Cl$ requires: C, 77·7, H, 5·4, Cl, 9·23%).

*Polynuclear dyes*

Indole (1·15 g) was dissolved in hot acetic anhydride (5 ml) and 50% hydrobromic acid in glacial acetic acid (0.81 ml) added. After the reaction had subsided the solution was refluxed for 2 min and *p*-dimethylaminobenzaldehyde (0·75 g) added. As the solution was refluxed for a further 3 min the orange colour gradually changed to a deep green. Addition of ether precipitated a green solid which was crystallized from methanol–ether to yield 3-indole-(4-dimethylaminobenzene)-3′-indole trimethincyanine bromide (1·5 g) as green needles m.p. 108° (Found: C, 69·0, H, 5·0, Br, 17.0; $C_{27}H_{24}N_3Br$ requires: C, 68·9, N, 5·1, Br, 17·0%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and 2-methyl-3-carbethoxy-4-phenyl-5-pyrrole aldehyde (1·3 g) were refluxed in glacial acetic acid (15 ml) for 1 hr when crystals deposited out of the purple solution. On crystallization from glacial acetic acid 3-(2-methylindole)-2′-(3-phenyl-4-carbethoxy-5-methylpyrrole)-α-3″-(2-methylindole) trimethincyanine chloride (1·1 g) was obtained as brassy octahedra m.p. 294° (Found: C, 75, H, 5·7, Cl, 6·5, $C_{25}H_{32}O_2N_2Cl$ requires: C, 74·73, H, 5·65, Cl, 6·3%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and 2-methyl-3-indole aldehyde (0·8 g) were refluxed in glacial acetic acid (15 ml) for 1 hr and the solution diluted with ether when a black solid was precipitated. On crystallization from acetic acid–ether, bis-3-(2-methylindole)-α-3′-(2-methylindole) trimethincyanine chloride (1·9 g) was obtained as black needles m.p. 247° (Found: C, 77·2, H, 5·7, Cl, 7·5; $C_{20}H_{21}N_2Cl$ requires: C, 77·11, N, 5·6, Cl, 7·66%).

α-Ethyl-2,2′-dimethyl-di-indolylmethene hydrochloride (1·8 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in glacial acetic acid–acetic anhydride mixture (15 ml) with vigorous stirring for 5 min and diluted with ether. The precipitate was crystallized from acetic acid–ether to give 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole)-β-methyl-trimethincyanine chloride (2·2 g) as dark blue needles. m.p. 300° (Found: C, 76·7, H, 6·2, Cl, 7·6, $C_{30}H_{30}N_3Cl$ requires C, 76·92, H, 6·41, Cl, 7·6%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in glacial acetic acid (15 ml) for 30 min and the blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride (2·0 g) as copper needles m.p. 221° (Found: C, 76·5, H, 6·0, Cl, 7·7; $C_{29}H_{28}N_3Cl$ requires: C, 76·65, H, 6·15, Cl, 7·83%).

α-Methyl-2,2′-diphenyl-di-indolylmethene hydrochloride (1·1 g) and 2-methyl-3-indole aldehyde (0·4 g) were refluxed in glacial acetic acid (15 ml) for 2 hr. On cooling solid was precipitated from the blue solution. On crystallization from glacial acetic acid 3-(2 methylindole)-3′-(2-phenylindole)-α-3″-(2-phenylindole) trimethincyanine chloride (0·5 g) was obtained as blue needles m.p. 258°. (Found: C, 81·4, H, 5·0, Cl, 6·0; $C_{40}H_{30}N_3Cl$ requires: C, 81·63, H, 5·1, Cl, 6·04%).

2,2′-Dimethyl-α-benzyl-di-indolylmethene hydrochloride (3·77 g) and *p*-dimethylaminobenzaldehyde (1·5 g) were refluxed in glacial acetic acid (30 ml) for 30 min and the blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole)-β-phenyl-trimethincyanine chloride (4·2 g) as black crystals m.p. 226°. (Found: C, 79·5, H, 6·3, Cl, 6·6; $C_{35}H_{32}N_3Cl$ requires: C, 79·24, H, 6.04, Cl, 6.7%).

α,α′-ethylene-bis-(2,2′-dimethyl-di-indolylmethene hydrochloride) (3·2 g) and *p*-dimethylaminobenzaldehyde (1·5 g) were refluxed in 1 : 1 glacial acetic acid–acetic anhydride mixture (30 ml) for 5 min and the ink-blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield β,β′-bis-[3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride] (3·5 g) as a dark blue powder m.p. 300°. (Found: C, 76·6, H, 6.3, Cl, 7·7; $C_{58}H_{54}N_6Cl_2$ requires: C, 76·9, H, 5·96, Cl, 7·83%).

α,2-Dimethyl-2′-phenyl-di-indolylmethene hydrochloride (2·4 g) and 2-methyl-3-indole aldehyde (1·0 g) were refluxed in glacial acetic acid–acetic anhydride mixture (20 ml) for 5 min and cooled. The brown solid which separated was crystallized from glacial acetic acid to yield bis-3-(2-methylindole)-α-3′-(2-phenylindole) trimethincyanine hydrochloride (0·5 g) as copper octahedra m.p. 198°. (Found: C, 79·6, H, 5·1, Cl, 6·6, $C_{38}H_{28}N_3Cl$ requires: C, 79·85, H, 5·32, Cl, 6·75%).

α,2-Dimethyl-2′-phenyl-di-indolylmethene hydrochloride (1·9 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in 1 : 1 glacial acetic acid–acetic anhydride mixture (20 ml) for 3 min and cooled. The solid which separated was crystallized from glacial acetic acid to yield 3-(2-phenylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride as copper brown needles, m.p. 238°. (Found: C, 79·2, H, 5·9, Cl, 6·7, $C_{34}H_{30}N_3Cl$ requires: C, 79·07, H, 5·81, Cl, 6·88%).

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# REACTIONS OF 2-(2′,4′-DINITROPHENYL)-AMINO-2-DEOXY-D-GLUCOSE, (DNP-D-GLUCOSAMINE), AND DERIVATIVES*

P. F. LLOYD and M. STACEY
Department of Chemistry, University of Birmingham

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Abstract—3,4,6-Tri-O-acetyl-2-amino-1-bromo-2-deoxy-α-D-glucose hydrobromide is of limited value for the synthesis of glycosides. Treatment of DNP-D-glucosamine with methanolic hydrogen chloride yielded a mixture containing a pyranoside and a furanoside. The stability of the N-dinitrophenyl group under acidic and alkaline conditions has been investigated and a method for its removal utilizing an anionic ion-exchange resin is described. An acetobromo derivative of DNP-D-glucosamine was obtained which reacted with alcohols to yield glycopyranosides which, in some cases, were of the α-configuration.

THE biologically-important glycosides of the amino-sugars cannot be obtained directly by acid-catalysed condensation of the sugar with an alcohol, a method commonly used to prepare glycosides of non-nitrogenous sugars. However, Irvine *et al.* obtained an acetobromo derivative,[1,2] 3,4,6-tri-O-acetyl-2-amino-1-bromo-2-deoxy-α-D-glucose hydrobromide (I), which on treatment with alcohols and pyridine, morphine, or silver carbonate[3] yielded β-glycosides. When this method was examined by us mercuric acetate was found to be a more effective catalyst, but even when this salt was employed as condensation agent and the products were separated by chromatography, yields of pure (methyl) glycoside never exceeded 50 per cent and were often considerably lower than this. Attempts to obtain a disaccharide by interaction of the bromo compound I and 1,2,3,4-tetra-O-acetyl-α-D-glucose were unrewarding: chromatographic analysis of the acetylated products on alumina or silica gel furnished crystalline derivatives of the monosaccharide starting materials and a large number of smaller amorphous fractions. It seems likely that there occurred *inter alia* condensation of the compound I with free amino groups to form disaccharides and higher polymers linked through N-glycoside bridges.

When the amino group of a hexosamine is acylated the resultant derivative resembles the aldohexoses in many of its reactions. Thus 2-acetamido-2-deoxy-D-glucose forms glycosides directly with alcohols and acid,[4] and also it can be converted to an acetobromo compound[5] which may be condensed with alcohols to yield β-glycosides. Unfortunately the removal of an N-acetyl group from the resultant glycoside, as in the case of methyl 2-acetamido-2-deoxy-α-D-glycopyranoside,[6] is attended by scission of glycosidic linkages when acid hydrolysis is used, and although

* For a preliminary account of part of this work see *Chem. & Ind.* 917 (1955).

[1] J. C. Irvine, D. McNicoll and A. Hynd, *J. Chem. Soc.* **99**, 250 (1911); J. C. Irvine and A. Hynd, *Ibid.* 41 (1913).

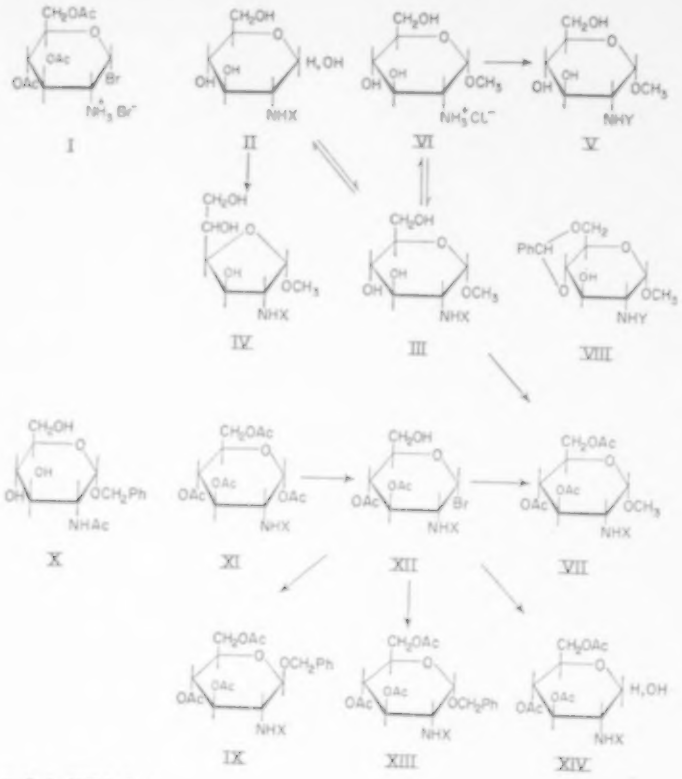
[2] F. Micheel, F. P. Van de Kamp and H. Wulff, *Chem. Ber.* **88**, 2011 (1955).

[3] M. L. Hamlin, *J. Amer. Chem. Soc.* **33**, 766 (1911).

[4] F. Zilliken, C. S. Rose, G. A. Braun and P. Gyorgy, *Arch. Biochem. Biophys.* **54**, 392 (1955).

[5] R. Kuhn and W. Kirshenlohr, *Chem. Ber.* **86**, 1331 (1953).

[6] A. B. Foster, D. Horton and M. Stacey, *J. Chem. Soc.* **81** (1957).




elimination of the acyl group under alkaline conditions is feasible, drastic conditions are required.[7] 2-Benzyloxycarbonylamino-2-deoxy-D-glucose is now often used for glycoside preparation because in this case the "blocking group" can be removed catalytically under very mild conditions when required. Regrettably, when attempts were made to prepare an acetobromo derivative of this compound, the hydrobromide I was obtained.[8]

The present work, a study of 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose (DNP-D-glucosamine, II) and its derivatives, was undertaken with the object of devising new methods for the synthesis of glycosides and oligosaccharides derived from aminosugars containing free, as well as substituted, amino groups. Earlier workers[9,10,11] had shown that on account of their crystalline properties and distinctive colour 2′,4′-dinitrophenyl-(DNP-) derivatives of hexosamine were very suitable for characterization and separation. In order to assess its value as a "blocking group" in the synthetic studies envisaged, information concerning the stability of

[7] P. W. Kent and M. W. Whitehouse, *Biochemistry of the Aminosugars* p. 232. Butterworths, London (1955).
[8] E. L. May and E. Mosettig, *J. Org. Chem.* **15**, 890 (1950).
[9] P. W. Kent, *Research* **3**, 427 (1950); P. W. Kent, G. Lawson and A. Senior, *Science* **113**, 354 (1951).
[10] K. H. Meyer and D. E. Schwartz, *Helv. Chim. Acta* **33**, 1651 (1950).
[11] E. F. Annison, A. T. James and W. T. J. Morgan, *Biochem. J.* **48**, 477 (1951).

the N-DNP group in hexosamines was sought together with a method for its removal which was mild and would not affect glycosidic linkages.

DNP-D-glucosamine (II) was prepared by treating 2-amino-2-deoxy-D-glucose hydrochloride with 1-fluoro-2,4-dinitrobenzene (FDNB) and sodium bicarbonate. A high yield of crude material was obtained which invariably suffered much loss on subsequent purification. Although some variation in experimental procedure was made the yield of pure product did not exceed 35 per cent.

On treatment of DNP-D-glucosamine (II) with methanolic hydrogen chloride at 65°, a complex mixture was obtained. The presence of some unchanged II was demonstrated chromatographically and fractional crystallization of the product eventually furnished small amounts of methyl 2-(2′,4-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside (III), $[\alpha]_D + 12{\cdot}7°$ and methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucofuranoside (IV), $[\alpha]_D + 30{\cdot}6°$. The identity of the pyranoside III was established by an alternative synthesis from methyl 2-benzyloxycarbonyl-amino-2-deoxy-α-D-glucopyranoside (V)[12] of known structure. The latter was converted to methyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride (VI) according to the directions of Neuberger and Rivers[12] and thence to III by condensation with FDNB. A crystalline derivative of II, methyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside (VII), was obtained on acetylation with pyridine and acetic anhydride.

From the value of its specific rotation it seemed unlikely that the glycoside IV was the anomeric form of the α-pyranoside III. Moreover the two glycosides were quite different in their susceptibilities to acid hydrolysis: whereas the substance IV was slowly hydrolysed to DNP-D-glucosamine (II) by 1N hydrochloric acid at room temperature, the α-pyranoside (III) was practically unaffected. The course of hydrolysis was followed polarimetrically and chromatographically. The substance IV was therefore tentatively assigned the furanoside structure indicated above since it is generally recognized that glycofuranosides are much more labile than glycopyranosides. Indeed the lability of the methyl 2-acetamido-2-deoxy-glucofuranoside obtained by Kent[9] established that the furanoside form of an N-substituted hexosamine displayed essentially the same ease of glycoside-breakdown as had been commonly observed with furanoside forms of non-nitrogeneous hexoses. The fact that the substance IV yielded 1 mole of formaldehyde on periodate oxidation gave support to the structure assigned. It should however be mentioned that in another experiment designed to determine the amount of periodate consumed, consistent results could not be obtained. Again, the isolation of a higher yield of IV (the only crystalline product isolated) when the acid-catalysed interaction of II and methanol was allowed to occur at room temperature was in accordance with the structure allocated to IV, corresponding as it did with the recognized tendency for furanoside structures to be formed under such mild conditions. From a consideration of the specific rotations of III and IV the latter is assumed to have the α-configuration. Compound IV formed a crystalline triacetate.

Treatment of the pyranoside III with 1N hydrochloric acid at 100° led to scission of the glycosidic linkage but the DNP group remained intact as judged from a chromatographic investigation of the hydrolysis: under alkaline conditions the DNP

[12] A. Neuberger and R. P. Rivers, *Biochem. J.* **23**, 1581 (1939); A. B. Foster, D. Horton and M. Stacey, *Chem. Soc.* 81 (1957).

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group was quickly eliminated with regeneration of the parent aminosugar glycoside. A convenient way of carrying out this alkaline hydrolysis consisted in treating the pyranoside III in aqueous–acetone with an anion-exchange resin (OH form). The resin not only effected the required de-dinitrophenylation but also retained the liberated 2,4-dinitrophenol. The product, methyl 2-amino-2-deoxy-α-D-glucopyranoside, which was obtained in excellent yield simply by filtration and evaporation, was characterized as the N-benzyloxycarbonyl-(V) and 4,6-O-benzylidene-N-benzyloxycarbonyl-(VIII) derivatives. This method of removal of the dinitrophenyl group was subsequently applied to other glycosides of II and in every case only the parent glucosamine derivative was isolated from the reaction products, there being no indication that scission of the (sugar) carbon-nitrogen linkage occurs to any significant extent.

The dinitrophenyl group was unaffected by treatment at room temperature with methanolic ammonia, a much-used reagent for de-O-acetylation. Thus benzyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)amino-2-deoxy-β-D-glucopyranoside (IX) the synthesis of which is described below, was smoothly deacetylated by this means. Subsequent alkaline (ion-exchange resin) hydrolysis of the deacetylation product furnished benzyl 2-amino-2-deoxy-β-D-glucopyranoside which was isolated as the N-acetyl derivative X by simultaneous O- and N-acetylation with acetic anhydride followed by de-O-acetylation with methanolic ammonia. The derivative X was identical with the benzyl 2-acetamido-2-deoxy β-D-glucopyranoside of known structure which was prepared from authentic benzyl 3,4,6-tri-O-acetyl-2-acetomida-2-deoxy-β-D-glucopyranoside[13] by de-O-acetylation.

The formation of an acetobromo derivative of DNP-D-glucosamine II was then attempted. 1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-α-D-glucose hydrochloride[14] was dinitrophenylated with FDNB and sodium carbonate, the product 1,3,4,6-tetra-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucose (XI) being obtained in good yield. An alternative method of arylation with FDNB and silver carbonate in chloroform solution gave the same product in lower yield. The compound XI was converted to 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-1-bromo-2-deoxy-α-D-glucose (XII) in near quantitative yield by treatment with HBr in glacial acetic acid and chloroform. This acetobromo compound XII is highly crystalline and can be kept in a dry atmosphere for several months without decomposition.

Concurrently with a study of the reactions of the bromo compound XII the syntheses of reference β-glycosides of known structures were carried out. The acetobromoglucosamine hydrobromide I of Irvine *et al.*[1] reacted with benzyl alcohol in the presence of pyridine forming benzyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucoside hydrobromide, which was converted to benzyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-β-D-glucoside (IX) by the usual method with FDNB. A parallel preparation of the corresponding β-methyl glycoside gave a syrupy product which, although analysing in the manner expected of methyl 3,4,6-O-acetyl-2-(2′, 4′-dinitrophenyl)-amino-2-deoxy-β-D-glucoside after chromatographic purification on alumina, could not be crystallized.

Treatment of the DNP acetobromo compound XII with benzyl alcohol in the presence of silver carbonate yielded the β-glucoside IX as expected, but a different

[13] W. O. Cutler and S. Peat, *J. Chem. Soc.* 274 (1939).
[14] L. Bergmann and M. Zervas, *Ber. Dtsch. Chem. Ges.* **64**, 975 (1931).

product XIII was obtained when the reaction was carried out in acetone solution with pyridine as condensation agent. From the fact that the new compound was non-reducing and in accordance with analytical and optical rotational data it was tentatively designated benzyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside. Under the conditions that appeared to favour the formation of the α-glycoside, a synthesis of methyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside (VII) was attempted by condensation of the bromo compound XII with methanol. On this occasion the product obtained was clearly of the α-configuration since it was identical with the authentic α-glycoside VII prepared as described above.

The yields of glycosides isolated after condensation of XII and an alcohol were not high and repeated recrystallization of the crude glycoside was necessary during the purification process. This was thought to be due, in part at least, to the presence in the reaction products of 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose (XIV); this compound was actually isolated during one experiment. Its structure was inferred from its reducing character and elemental analysis data.

It seems clear from these investigations that DNP-D-glucosamine and derivatives are potentially of considerable value for glycoside formation and other synthetic operations in the glucosamine field. A detailed consideration of the reactions of the bromo compound XII will be presented in a subsequent communication.

## EXPERIMENTAL

*Paper chromatography.* The upper phase of a water : 1-butanol : ethanol (5 : 4 : 1 by volume) mixture was used as mobile phase for paper chromatography and all $R_F$ values given below refer to this solvent system.

In all reactions involving bromo compounds dry reactants were used and rigorously anhydrous conditions were observed.

*2-(2′,4′-Dinitrophenyl)-amino-2-deoxy-D-glucose*

2-Deoxy-2-amino-D-glucose hydrochloride (2·00 g), sodium carbonate (0·98 g) and 1-fluoro-2,4-dinitrobenzene in acetone : water (50 ml, 1 : 4 v/v) were shaken overnight. The acetone was removed by evaporation under reduced pressure and the residue washed with ice-water (45 ml) and dried. The crude product (80% yield) was dissolved in hot methanol and 4–5 volumes of benzene and sufficient light petroleum (b.p. 60–80) to produce turbidity added. On standing the product (1·12 g, 35% separated as orange needles m.p. 194–196°, $[\alpha]_D^{13}$ 4 + 1·2° (*c*. 1·0 in ethanol) + 63·7 (*c*. 0·8 in 80% (v/v) ethanol, $R_F$ 0·82. Kent[9] reports m.p. 167–169, $[\alpha]_D^{22}$ + 50° (ethanol), Meyer and Schwartz,[10] m.p. 196 ± 2° and Annison *et al.*[11] give m.p. 202–204, $[\alpha]_{5461}$ + 65 ± 3° (80% (v/v) ethanol).

*Reaction of 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose with methanolic hydrogen chloride*

(a) *At* 65°. A solution of 2-(2′,4′-dinitrophenyl)-2-amino-2-deoxy-D-glucose (5·0 g) in dry methanol (250 ml) containing 2·1% hydrogen chloride was heated under reflux until the optical rotation became constant, $[\alpha]_D^{20}$ + 48·0° (5 min) → + 55·0° (80 min). The solution was neutralized with silver oxide, filtered, treated with hydrogen sulphide, filtered and evaporated to a yellow syrup. This was dissolved in acetone and 4 volumes of ether and light petroleum (b.p. 80–100°) added until the solution was turbid. On standing, yellow prisms (Fraction A, 1·15 g), m.p. 201–204°, were deposited. From the mother liquors, after evaporation, dissolution in ethanol and addition of water at 0° a second crystalline fraction (Fraction B, 1·07 g), m.p. 95° unsharply, was obtained. Evaporation of the mother liquors and tritration with ethanol : light petroleum furnished a third crystalline fraction (Fraction C, 0·42 g) m.p. 134–136°.

Repeated recrystallization of fraction A from ethanol : light petroleum and from aqueous acetone afforded yellow prisms of *methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside* (0·21 g),

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m.p. 216–218°, $[\alpha]_D^{19}$ + 12·7° (*c* 1·0 in acetone), $R_F$ 0·88 (Found: C, 43·5, H, 4·9; N, 11·3. $C^{13}H_{17}O_9N_3$ required: C, 43·7; H, 4·8, N, 11·7; OMe, 8·6%).

After many recrystallizations of fraction B from ethanol : light petroleum, yellow prisms of *methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucofuranoside* (0·31 g) were obtained. This compound had m.p. 166–167°, $[\alpha]_D^{18}$ + 30·6° (*c* 1·0 in acetone) $R_F$ 0·88 and was generally more soluble in water and organic solvents than the corresponding pyranoside. (Found: C, 43·8; H, 4·7; N, 11·9, mol. wt. (Rast) 350. $C_{13}H_{17}O_9N_3$ requires: C, 43·7; H, 4·8; N, 11·7%; mol. wt. 359).

Oxidation of the furanoside with unbuffered aqueous 0·3 M sodium metaperiodate for 1½ hr followed by distillation[16] and treatment of the distillate with dimedone gave a precipitate (m.p. 188–189°) which corresponded to the formation of 0·96 mole formaldehyde.

The melting point of fraction C had not become constant after six recrystallizations. The product (0·030 g) then had m.p. 198–206°, $[\alpha]_D^{17}$ + 7·8 (*c* 0·5 in acetone), $R_F$ 0·89.

Chromatographic examination of the mother liquors indicated that some unchanged starting material was present.

(b) *At room temperature.* A solution of 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose (0·500 g) in dry methanol (25 ml) containing 2·1% hydrogen chloride underwent a slow change in optical rotation which became constant after 14 days. $[\alpha]_D^{19}$ + 48·0 (zero time) → $[\alpha]_D^{18}$ 58·5° (14 days). The solution was neutralized with silver oxide, filtered and evaporated to dryness. The residue on dissolution in ethanol and addition of petroleum ether (b.p. 80–100°) furnished some crystalline material. Repeated recrystallization of the latter yielded methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucofuranoside (0·082 g) m.p. 166–167°.

*Methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside*

Methyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride[18] (0·41 g), 1-fluoro-2,4-dinitro benzene (0·50 g) and sodium carbonate (0·19 g) in acetone : water (10 ml, 4 : 1 v/v) were shaken for 48 hr. After removal of the acetone by evaporation the residue was washed with ice-water and recrystallized from ethanol. The product (0·41 g, 65%) was identical with the product derived from fraction A (above). (Found: C, 43·9; H, 4·9; N, 11·7; oMe, 9·6%).

*Acid hydrolysis of methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucosides*

(a) *At room temperature.* Each glycoside (0·050 g) in acetone (4·0 ml) was treated with 5N hydrochloric acid (1·0 ml) and kept at room temp. The reaction was followed polarimetrically and also by chromatographic examination of aliquots at suitable intervals. The furanoside ($R_F$ 0·89) was slowly hydrolysed and after 50 days 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose, but only a trace of the original furanoside, was detected chromatographically. The optical rotation had become constant. $[\alpha]_D^{20}$ + 63·7 → + 47·4°. Evaporation and recrystallization gave 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose.

The pyranoside remained unhydrolysed and was recovered unchanged (91%) after 50 days. 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose when subjected to the above acid treatment underwent no change, polarimetrically or chromatographically.

(b) *At* 100°. The hydrolysis of methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucofuranoside by 1·0N hydrochloric acid was followed chromatographically. After 2 hr, from the intensities of the spots about 30% of the glycoside had been hydrolysed. After 7 hr an intense spot corresponding to 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-D-glucose was seen and only a trace of the starting material. After development of the chromatogram with silver nitrate : sodium hydroxide sprays, no further spots appeared.

*Methyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside*

Methyl 2-(2′4′-dinitrophenyl)-amino-2-deoxy-α-D-glucopyranoside (0·103 g) was dissolved in acetic anhydride (1·0 ml) and pyridine (1·0 ml). After standing for 3 days at room temp the mixture was poured into a large volume of water and the yellow precipitate filtered and recrystallized from ethanol. The *tri-acetyl derivative* (0·109 g, 817%), needles, had m.p. 206°, $[\alpha]_D^{18}$ + 21·3° (*c* 0·5 in chloroform), $[\alpha]_D^{18}$ + 71·6 (*c* 0·5 in acetone) (Found: C, 46·9; H, 5·1; N, 8·7; $C_{19}H_{22}O_{12}N_4$ requires: C, 47·0; H, 4·8; N, 8·7%).

*Methyl* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-amino-2-*deoxy*-α-D-glucofuranoside

This compound (79% yield) was obtained by acetylation of methyl 2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucofuranoside by the method described above. Recrystallized from ethanol *the product* had m.p. 95–97°, $[\alpha]_D^{22}$ +99·7 (*c* 0·7 in chloroform), $R_F$ 0·95. (Found: C, 47·3; H, 4·6; N, 8·9. $C_{19}H_{22}O_{12}N_4$ requires: C, 47·0; H, 4·8; N, 8·7%).

*Methyl* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-amino-2-*deoxy*-β-D-*glucopyranoside*

Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrobromide (0·50 g) prepared according to the method of Irvine *et al.*,[1] 1-fluoro-2,4-dinitrobenzene (0·35 g), sodium carbonate (0·133 g), acetone (8 ml) and water (2 ml) were shaken together for 24 hr. The acetone was removed by distillation and the residue extracted with ether. After washing with dil hydrochloric acid and water the ethereal solution was evaporated to a bright yellow syrup, (0·749 g) which gave a single discrete spot, $R_f$ 0·95, on the paper chromatogram. This could not be crystallized and charring occurred when distillation in a high vacuum was attempted on part of the product. It was purified by chromatography on an alumia column eluting successively with benzene : light petroleum (b.p 60–80°) (1 : 1 v/v), other mixtures of benzene and light petroleum containing higher proportions of benzene, benzene : chloroform (1 : 1 v/v) and benzene : chloroform (1 : 2 v/v). *Methyl* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-β-D-*glucopyranoside* (80% yield) was obtained as a light yellow syrup $[\alpha]_D^{22}$ +58·1 (*c*, 0·9 in acetone). (Found: C, 47·5; H, 5·1; N, 8·8. $C_{19}H_{22}O_{12}N_4$ requires: C, 47·0; H, 4·8; N, 8·7%).

*Benzyl* 3,4,6-*tri*-O-*acetyl*-2-*amino*-2-*deoxy*-β-D-*glucopyranoside hydrobromide*

This compound was prepared by a modification of the method of Cutler and Peat,[12] 3, 4, 6-Tri-O-acetyl-2-amino-1-bromo-2-deoxy-α-D-glucose hydrobromide (1·00 g) was dissolved in benzyl alcohol (10 ml) and containing 2% anhydrous pyridine. After standing at room temp overnight, light petroleum (b.p. 80–100°): ether (80 ml, 3 : 1 v/v) was added and the gelatinous precipitate filtered off and suspended in ethyl acetate (25 ml). After filtering and washing with ether, recrystallization of the solid from ethanol : light petroleum afforded fine needles of the *benzyl glycoside* (0·443 g, 42%), which decomposed without melting at 237–241°, $[\alpha]_D^{23}$ +19·5° (*c* 0·5 in chloroform) (Found: C, 47·9; H, 5·4; N, 2·9. Calc. for $C_{15}H_{20}O_6NBr$: C, 47·9, H, 5·5; N, 3·0%). Cutler and Peat[12] give decomp 237–240°, $[\alpha]_D^{14}$ +24·2 (*c* 1.0 in chloroform).

*Benzyl* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-β-D-*glucopyranoside*

The benzyl glycoside prepared above (0·15 g) was shaken with 1-fluoro-2,4-dinitrobenzene (0·088 g) and sodium bicarbonate (0·056 g) in 80% (v/v) aqueous acetone (5 ml) for 14 hr. Evaporation, crystallization by trituration with ethanol and recrystallization from the same solvent furnished the *dinitrophenylated compound*, large yellow prisms, (0·15 g, 85%), m.p. 160°, $[\alpha]_D^{22}$ +44·1° (*c* 1·0 in chloroform). (Found: C, 53·4; H, 4.7; N, 7·8 ($C_{25}H_{27}O_{13}N_4$ requires: C, 53·5; H, 4·9; N, 7·5%).

*Benzyl* 2-*acetamido*-2-*deoxy*-β-D-*glucopyranoside*

Benzyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrobromide (0·055 g) was dissolved in pyridine (1·2 ml) and acetic anhydride (1·0 ml). After 3½ hr the mixture was poured into ice-water and the precipitate recrystallized from ethanol to give benzyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (0·035 g, 70%), m.p. 163°, $[\alpha]_D^{18}$ —42·3 (*c* 0·3 in chloroform). Kuhn *et al.*[5] give m.p. 165–167°, $[\alpha]_D^{20}$ —43·4 (in methanol) for this compound.

On de-O-acetylation with methanolic ammonia the tri-O-acetyl-derivative was converted to benzyl 2-acetamido-2-deoxy-β-D-glucopyranoside (70% yield) m.p. 204–206° $[\alpha]_D^{19}$ —45·2 (*c* 0·4 in water). Kuhn *et al.*[5] give m.p. 205–206°, $[\alpha]_D$ —48° (in water).

*Benzyl* 2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-β-D-*glucopyranoside*

The tri-O-acetyl-derivative of this compound (0·200 g) was deacetylated by dissolving in dry methanol (20 ml) which had been saturated with ammonia at 0° and acetone (7 ml) and keeping

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at room temp overnight. The solvents were removed by evaporation and the residue recrystallized from ethanol : light petroleum (b.p. 80–100°). The *product* of deacetylation (0·072, 50%) had m.p. 198°. (Found: C, 52·7; H, 4·7; N, 9·4. $C_{19}H_{21}O_9N_3$ requires: C, 52·4; H, 4·9; N, 9·6%).

*Alkaline (resin) hydrolysis of derivatives of* 2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-D-*glucose*

(a). *Methyl* 2-(2′4′-*dinitrophenyl*)-*amino*-2-*deoxy*-α-D-*glucopyranoside*. When this compound (0·200 g) was dissolved in acetone : water (10 ml, 2 : 1 v/v) and Amberlite "IRA-400-OH" (9 g) added and the mixture shaken rapid decolorization occurred. After shaking overnight the filtered solution was evaporated *in vacuo* to syrupy methyl 2-amino-2-deoxy-D-glucopyranoside (0·120 g). This was characterized by formation of the benzyloxycarbonyl- and benzylidene-benzyloxycarbonyl-derivatives as follows.

The syrupy product (0·120 g) was dissolved in water (1·2 ml) and sodium bicarbonate (0·094 g) added. Benzyloxycarbonyl chloride (0·152 g) was added dropwise over a period of 1 hr with vigorous shaking during the whole period. After 70 min the mixture was cooled to 0° for 2 hr and the crystalline methyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (0·091 g, 50%) separated. This had m.p. 160–161°, $[\alpha]_D$ +96·4° (*c* 1·0 in pyridine). The melting point was not depressed on admixture with an authentic specimen.[13] (Found C, 54·5; H, 6·5; N, 4·3. Calc. for $C_{15}H_{21}O_7N$: C, 55·0; H, 6·5, N, 4·3%).

The benzyloxycarbonyl derivative[15] (0·016 g) was stirred with freshly distilled benzaldehyde (0·13 ml) and zinc chloride (fused) (0·020 g) until solution was complete. After standing overnight three vol of ethanol were added. The precipitate was recrystallized from acetone which afforded five needles of *methyl* 4,6-0-*benzylidene*-2-*benzyloxycarbonylamine*-2-*deoxy*-α-D-*glucopyranoside* (0·014 g, 69%), m.p. 212–213° (Found: C, 64·1; H, 6·4; $C_{23}H_{25}O_7N$ requires: C, 63·6; H, 6·1%).

(b). *Benzyl* 2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-β-D-*glucopyranoside*. This compound (0·20 g) was dedinitrophenylated with "Amberlite IRA 400-04" by the method described above. The product, a syrup, (0·058 g, 47%) was N-acetylated by treatment with dry methanol : acetic anhydride (1·5 ml, 8 : 1 v/v) at room temp overnight. On evaporation and recrystallization of the residue, white needles of benzyl 2-acetamido-2-deoxy-β-D-glucoside (0·026 g, 43%) were obtained identical with an authentic sample, the preparation of which is described above.

1,3,4,6-*Tetra*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-α-D-*glucose*

(a). *Reaction in aqueous acetone solution.* 1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-2-D-glucose hydrochloride (1·00 g) m.p. 230° (decomp), $[\alpha]_D^{23}$ +29·9 (*c* 1·2 in water), which had been prepared by the method of Bergmann and Zervas[14] was shaken with 1-fluoro-2,4-dinitrobenzene (0·49 g) and sodium bicarbonate (0·22 g) in acetone (16 ml) and water (4 ml) for 14 hr at room temp. The solution was concentrated to a small volume and the solid that separated recrystallized from ethanol yielding lemon needles of 1,3,4,6-*tetra*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-α-D-*glucose* (1·12 g, 84%), m.p. 166–167°, $[\alpha]_D^{19}$ +47·9 (*c* 1·0 in chloroform), $R_F$, 0·95 (Found: C, 46·7; H, 4·2; N, 8·2; $C_{20}H_{23}O_{15}N_3$ requires: C, 46·8; H, 4·5; N, 8·2%).

(b). *Reaction in chloroform solution.* A solution of 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-α-D-glucose (1·00 g), m.p. 141°[14], and 1-fluoro-2,4-dinitribenzene (0·51 g) in dry chloroform (20 ml) was shaken with dry silver carbonate (2.15 g) for 24 hr. The solution was filtered, evaporated, and the residue on recrystallization furnished the same product as obtained in (a). Yield 36%.

3,4,6-*Tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-1-*bromo*-2-*deoxy*-α-D-*glucose*

1,3,4,6-Tetra-O-acetyl-2-(2′,4′-dinitrophenyl)-2-deoxy-α-D-glucose (2·90 g) was dissolved in a mixture of glacial acetic acid (45 ml) which had been saturated with dry HBr at 0° and chloroform (25 ml), and dry HBr was passed through the solution for 30 min. After standing for 2 hr at room temp the mixture was poured into ice-water and extracted with chloroform. The chloroform extract was washed with ice-cold sodium bicarbonate solution until free from acid, then washed with water, dried ($MgSO_4$) and evaporated under diminished pressure. The yellow residue, which crystallized spontaneously was the *bromo compound* (2·90 g, 96%); it was of a high degree of purity, m.p. 160–162°, $[\alpha]_D^{19}$ +45·6 (*c* 0·8 in chloroform) (Found: Br 14·4%). It was usually recrystallized from dry acetone–light petroleum (b.p. 100–120°) before further use when it (2·38 g) had m.p. 162–164°

[15] Z. Y. Kyi, Ph.D. Thesis, Birmingham (1951).

$[\alpha]_D^{19}$ + 46·0. It could also be recrystallized from glacial acetic acid or benzene, and was soluble in chloroform, acetone, ether and alcohols and insoluble in light petroleum and water. Normally, the compound was stored in a desiccator but a sample exposed to the atmosphere for several days suffered no decomposition. (Found: C, 40·6; H, 3·8; N, 8·1; Br, 14·8. $C_{18}H_{20}O_{11}N_2Br$ requires: C, 40·5; H, 3·8; N, 7·9; Br 14·8%).

*Reaction of* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-1-*bromo*-2-*deoxy*-α-D-*glucose with alcohols*

(a) *With benzyl alcohol in the presence of silver carbonate.* A solution of the bromo compound (0·50 g) and benzyl alcohol (1·0 ml) in chloroform (10 ml) was stirred with silver carbonate (2·6 g) and anhydrous calcium sulphate (1·0 g) for 45 hr in the dark. The solution was filtered through a charcoal mat and evaporated to dryness. Trituration with ethanol caused crystallization and recrystallization from the same solvent gave yellow prisms of benzyl 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-β-D-*glucoside* (0·22 g, 41%), m.p. 160° unchanged on admixture with authentic material. (Found: C, 53·4; H, 4·9; N, 7·4%).

Evaporation of the mother liquors from the above recrystallization yielded a solid m.p. 125–130°. Repeated recrystallization from light petroleum (b.p. 60–80°) : ethyl acetate and from ethanol gave yellow needles of 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-D-*glucose* (0·028 g), m.p. 150–152·5 depressed to 128–136° when mixed with the β benzyl glycoside (above). It reduced ammoniacal silver nitrate. (Found: C, 45·6; H, 4·6; N, 8·4. $C_{18}H_{21}O_{13}N_3$ requires: C, 45·9; H, 4·5; N, 9·0%).

(b) *With benzyl alcohol in the presence of pyridine.* The bromo compound (0·072 g) was mixed with benzylalcohol (2·0 ml) containing 1% pyridine, acetone (1·0 ml) added to effect complete solution, and the reaction followed polarimetrically $[\alpha]_D^{19}$ + 100° (40 min) → + 69·2° (2 hr) → + 9·2 (14 hr) (constant). After 20 hr the acetone was removed by distillation and the remaining solution poured into light petroleum (40 ml, b.p. 40–60°) containing 4% ethanol. The precipitate which separated, on recrystallization from ethanol yielded *benzyl* 3,4,6-*tri*-O-*acetyl*-2-(2′,4′-*dinitrophenyl*)-*amino*-2-*deoxy*-α-D-*glucoside* (0·023 g, 30%), yellow needles, m.p. 198–200° (sintering at 180°), $[\alpha]_D^{19}$ + 9·0° (*c* 0·3 in chloroform). (Found: C, 53·0; H, 4·8; N, 7·9. $C_{25}H_{27}O_{12}N_3$ requires: C, 53·5; H, 4·8; N, 7·5%).

(c) *With methanol in the presence of pyridine.* Condensation of the bromo compound (0·12 g) with methanol (1·8 ml) by the method described in (b) above furnished methyl 3,4,6-tri-O-acetyl-2-(2′,4′-dinitrophenyl)-amino-2-deoxy-α-D-glucoside (0·045 g 45%), m.p. 206°, alone and when mixed with authentic material, $R_F$ 0·95.

This investigation was supported by grants from the Nuffield Foundation to which one of us (P.F.L.) is indebted for a Research Studentship and a Fellowship.

[16] P. Karrer and K. Pfaehler, *Helv. Chim. Acta* **17**, 766 (1934).

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# THE STRUCTURE OF GALACTOSYL-LACTOSE, A TRISACCHARIDE PRODUCED FROM LACTOSE BY *PENICILLIUM CHRYSOGENUM* THOM

A. BALLIO and S. RUSSI
Istituto Superiore di Sanità, International Research Centre for Chemical Microbiology, Rome, Italy

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**Abstract**—Galactosyl-lactose, the main oligosaccharide synthesized from lactose by the transgalactosylase of *Penicillium chrysogenum* Thom, is O-β-D-galactopyranosyl-(1 → 6)-O-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose.

SEVERAL reducing oligosaccharides are formed when a cell-free extract of *Penicillium chrysogenum* Thom acts on lactose.[1] The main product of this reaction besides glucose is a trisaccharide (galactosyl-lactose), resulting from enzymic transfer to lactose of a galactosyl residue from a second lactose molecule. In the present paper a complete structural proof of this compound is presented. A preliminary report has been published elsewhere.[2]

Galactosyl-lactose has been prepared in gram amounts from the filtrates of *P. chrysogenum* grown on lactose-containing media. In fact it was shown in a recent study[3] that most of the oligosaccharides synthesized from lactose by enzymic preparations of the mould are also produced in such media, which represent a much more convenient source for isolation purposes. Fractionation of the complex mixture of sugars was achieved by column chromatography on cellulose or on charcoal–celite,[4] galactosyl-lactose being finally purified by acetone precipitation from methanolic solutions.

Molecular weight determinations by two independent methods confirmed the trisaccharide structure. Acid hydrolysis to completion resulted in the liberation of galactose and glucose in the approximate ratio of 2 : 1. Paper chromatography of the products of partial acid hydrolysis showed, besides glucose, two disaccharides, lactose and 6-O-β-D-galactopyranosyl-D-galactopyranose. Alkaline hypoiodite oxidation of the trisaccharide, followed by acid hydrolysis, resulted in the formation of galactose as the only reducing monosaccharide and of gluconic acid. Final proof of the structure of galactosyl-lactose was obtained by determining the nature of the compound obtained by acid hydrolysis of its undecamethylether. Gradient elution with water-methyl ethyl ketone on a charcoal–celite column[5] separated the mixture of methylated sugars very satisfactorily into three fractions (Fig. 1). These corresponded to approximately equimolecular proportions of 2,3,4-tri-O-methyl-D-galactose, 2,3,6-tri-O-methyl-D-glucose and 2,3,4,6-tetra-O-methyl-D-galactose. The methylated hexoses

[1] A. Ballio, E. B. Chain and F. Dentice di Accadia, *Rend. Ist. Sup. Sanità* **18**, 1183 (1955).
[2] A. Ballio and S. Russi, *Boll. Soc. Ital. Biol. Sperim.* **33**, 1748 (1957).
[3] A. Ballio and S. Russi, *J. Chromatography* In press.
[4] R. L. Whistler and D. F. Durso, *J. Amer. Chem. Soc.* **72**, 677 (1950).
[5] B. Lindberg and B. Wickberg, *Acta Chem. Scand.* **8**, 569 (1954).

were identified by determining their optical rotation, their paper chromatographic mobility and the melting point of their aniline derivatives.

The low positive values of the optical rotation of the trisaccharide and of the two disaccharides obtained from it by partial acid hydrolysis, indicated a $\beta$-configuration of both galactosidic linkages. Such a configuration for the new galactosidic linkage in galactosyl-lactose could also be predicted on the basis of the general observation that in transglycosylation reactions the transferred residue retains the anomeric

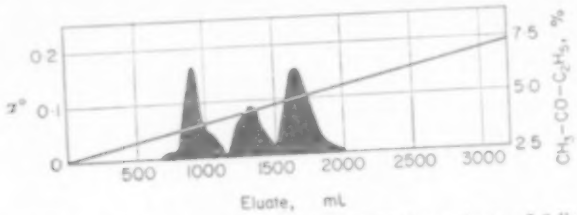


FIG. 1. Separation on charcoal-celite of the acid hydrolysis products of fully methylated galactosyl-lactose. The peaks, from left to right, correspond to 2,3,4-tri-O-methyl-D-galactose, 2,3,6-tri-O-methyl-D-glucose, 2,3,4,6-tetra-O-methyl-D-galactose.

linkage initially present in the substrate sugar. Further evidence for the $\beta$-configuration was obtained from the value of the molar optical rotation of the trisaccharide (+18,360). This differs markedly from the value which may be calculated for an $\alpha$-1,6-linked galactosyl-lactose (+56,920) by the summation of the molar rotation of lactose (+17,920) and the generally accepted[6] rotatory contribution of the $\alpha$-D-galactopyranosyl unit to various sugars (+39,000). The configuration of the glycosidic linkages was further confirmed by the infra-red spectrum (in Nujol) of the trisaccharide in the range 700–1000 $cm^{-1}$, where the most characteristic frequencies of carbohydrates occur.[7] In fact, peaks typical of $\beta$-linkages were observed (779 and 900 $cm^{-1}$), whereas in the region where $\alpha$-linkages give rise to well defined peaks (800–850 $cm^{-1}$) a broad minimum was noted.

All results lead to the conclusion that the galactosyl-lactose synthesized from lactose by cell-free extracts or growing cultures of *P. chrysogenum* is 6-O-$\beta$-D-galactopyranosyl-(1 → 6)-O-$\beta$-D-galactopyranosyl-(1 → 4)-D-glucopyranose.

An identical structure has been proposed by Pazur for the main trisaccharide formed during the hydrolysis of lactose by enzymic preparations from lactose-fermenting yeasts,[8] but no confirmatory evidence for it has so far been published. Wallenfels, *et al.*[9] had also observed the formation of a galactosyl-lactose ('lactotriose') when the $\beta$-galactosidases from *Escherichia coli*, *Aspergilli*, *Helix pomatia* or calf intestine, act on lactose. Only in the case of *Aspergilli* was an analytically pure trisaccharide isolated;[10] since no physico-chemical constants were reported for this fungal metabolite, it is not possible to ascertain if it possesses the same structure as the galactosyl-lactose formed by *P. chrysogenum*.

The results of this chemical study, together with the early finding that the galactosyl-lactose produced by *P. chrysogenum* represents the major and first oligosaccharide

[6] D. French, *Advanc. in Carbohydrate Chem.* **9**, 160 (1954).
[7] S. A. Barker, E. J. Bourne and D. H. Whiffen, *Methods of Biochemical Analysis* Vol. III, p. 213. Academic Press, New York (1956).
[8] J. H. Pazur, *Science* **117**, 355 (1953); *J. Biol. Chem.* **208**, 439 (1954).
[9] K. Wallenfels, E. Bernt and G. Limberg, *Liebigs Ann.* **584**, 63 (1953).
[10] K. Wallenfels, E. Bernt and G. Limberg, *Liebigs Ann.* **579**, 113 (1953).

synthesized by the mould during the course of lactose hydrolysis, indicate that the formation of $\beta$-1,6-galactosidic linkages is favoured in this enzymic reaction. It is relevant that a preponderant transfer of the non-reducing residue of disaccharides to primary alcoholic groups of acceptor molecules has been observed with other fungal transglycosylases.[11]

## EXPERIMENTAL

Melting points are not corrected. Paper chromatography was carried out on Whatman No. 1 paper by the descending method with the following solvent systems: (a) n-butanol-pyridine-water

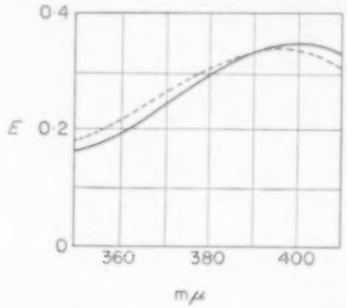


FIG. 2. Ultra-violet absorption spectra of ethanolic solutions ($2 \times 10^{-5}$ molar) of glucosazone and galactosyl-lactosazone.
– – – – – – – – – Glucosazone, ———————— Galactosyl-lactosazone.

(6 : 4 : 3, by volume); (b) n-butanol–98 per cent formic acid–water (4 : 1·8 : 4, by volume); (c) n-butanol saturated with water; (d) n-butanol–acetic acid–water (4 : 1 : 5, by volume, top layer); (e) n-butanol–ethanol–ammonia ($d = 0{\cdot}92$)–water (40 : 10 : 1 : 49, by volume, top layer). Sugars were detected with a benzidine–trichloroacetic acid spray,[12] gluconic acid with bromophenol blue in ethanol (0·04%).

*Isolation of galactosyl-lactose.* This was prepared by a procedure described in detail in another paper,[2] which also reports data showing that the trisaccharide prepared from culture filtrates of *P. chrysogenum* grown on lactose-containing media is identical with that isolated from lactose solutions incubated with a cell-free preparation of the same mould. After column chromatography the fractions containing the trisaccharide were evaporated *in vacuo*, taken up in the minimal amount of hot methanol, warmed with charcoal to decolourize and filtered hot. The solution was kept warm and hot acetone was added until a cloudiness appeared. After standing two days at 5° the white precipitate was centrifuged, washed several times with cold acetone and dried at room temperature *in vacuo*. The material showed $[\alpha]_D^{20}$ of $+34°$ (*c*, 1 in $H_2O$) and a m.p. 187°, sintering at 167°. (Found: C, 39·66: H, 6·70. Calc. for $C_{18}H_{32}O_{16}{\cdot}2H_2O$; C, 40·0; H, 6·71%). Molecular weight determined by hypoiodite oxidation.[13] (Found: 560. Calc. for $C_{18}H_{32}O_{16}{\cdot}2H_2O$: 540); also spectrophotometrically[14,15] by comparing the absorbancy of an ethanolic solution of the trisaccharide osazone with that of an ethanolic solution of glucosazone (Fig. 2). The osazones were prepared by standard procedures; that of the trisaccharide crystallized from ethanol–water mixtures as long needles m.p. 229–231°.

[11] S. C. Pan, L. W. Nicholson and P. Kolachov, *J. Amer. Chem. Soc.* **73**, 2547 (1951); *Arch. Biochem. Biophys.* **42**, 406 (1953); J. H. Pazur and D. French, *J. Amer. Chem. Soc.* **73**, 3536 (1951); *J. Biol. Chem.* **196**, 265 (1952); J. S. D. Bacon and D. J. Bell, *J. Chem. Soc.* 2528 (1953); D. J. Bell and J. Edelman, *Ibid.* 4652 (1954); N. Albon, D. J. Bell, P. H. Blanchard, D. Gross and J. R. Rundell, *Ibid.* 24 (1953); D. Gross, P. H. Blanchard and D. J. Bell, *Ibid.* 1727 (1954); S. A. Barker and T. R. Carrington, *Ibid.* 3588 (1953); S. A. Barker, E. J. Bourne and T. R. Carrington, *Ibid.* 2125 (1954); S. A. Barker, E. J. Bourne, G. C. Hervitt and M. Stacey, *Ibid.* 3734 (1955); S. A. Barker, E. J. Bourne and O. Theander, *Ibid.* 2064 (1957); K. Saroja, R. Venkataraman and K. V. Giri, *Biochem. J.* **60**, 399 (1955); A. Ballio and S. Russi, *Gazz. Chim. Ital.* **86**, 476 (1956); E. M. Crook and B. A. Stone, *Biochem. J.* **65**, 1 (1957).

[12] J. S. D. Bacon and J. Edelman, *Biochem. J.* **48**, 114 (1951).

[13] R. Willstätter and G. Schudel, *Ber. Dtsch. Chem. Ges.* **51**, 780 (1918).

[14] R. Kuhn, H. H. Baer and A. Gauhe, *Ber. Dtsch. Chem. Ges.* **88**, 1135 (1955).

[15] V. C. Barry, J. E. McCormik and P. W. D. Mitchell, *J. Chem. Soc.* 222 (1955).

*Complete hydrolysis.* The trisaccharide (5 mg) was heated with sulphuric acid (1 N, 0·5 ml) in a sealed tube at 110° for 2 hr. The cooled solution was neutralized with Amberlite resin IRA–400 and examined by quantitative paper chromatography. The chromatograms were run with solvent (a), and the monosaccharides were eluted with water and estimated by the micromethod of Nelson.[16] A glucose-galactose ratio of 1 : 1·8 was found.

*Partial hydrolysis.* The trisaccharide (50 mg) was heated with acetic acid (2 N, 25 ml) in a sealed tube at 110° for 9 hr. Examination by paper chromatography (solvent a) indicated the presence of glucose, galactose, lactose and 6-O-β-D-galactopyranosyl-D-galactose, as reported previously.[3] After removing the acetic acid *in vacuo* below 35°, the solution was neutralized with Amberlite resin IR-4B

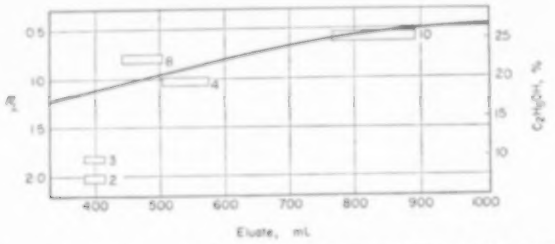


FIG. 3. Emergence from a charcoal-celite column of sugars formed by the partial hydrolysis of galactosyl-lactose. No. 2, galactose, No. 3, glucose, No. 4, lactose, No. 8, 6-O-β-D-galactopyranosyl-D-galactose, No. 10, galactosyl-lactose. $R_L$ is the ratio of the distance moved on paper chromatography (solvent a) by each substance, to that moved by lactose. The numbers assigned to the sugars correspond to those used in another paper.[3]

and then fractionated on a charcoal-celite column by gradient elution with ethanol.[3] A column 3 cm wide and 38 cm high was used, with a mixer containing 500 ml 5% ethanol and a reservoir with 1000 ml 30% ethanol. Fractions of 6 ml were collected with a fraction collector. Paper chromatography of individual fractions with solvent (a) showed that a partial separation of the two disaccharides had been obtained (Fig. 3). These were isolated by evaporation of appropriate fractions *in vacuo* and further purified by paper chromatography with solvent (a). As shown in Table 1, the paper chromatographic mobilities of the homogeneous disaccharides in solvents (a) and (d) were identical to those of authentic lactose and 6-O-β-D-galactopyranosyl-D-galactose (generously donated by Dr. B. Lindberg). The products had respectively $[\alpha]_D^{24}$ +52·0° (*c*, 1 in $H_2O$) (lactose $[\alpha]_D^{24}$ +52·4°), and $[\alpha]_D^{24}$ +29·3° (*c*, 1 in $H_2O$) (Bouveng and Lindberg[17] report $[\alpha]_D^{20}$ +30° for 6-O-β-D-galactopyranosyl-D-galactose).

*Hypoiodite oxidation.* The trisaccharide (10 mg in 1 ml $H_2O$), iodine (6 mg) and potassium hydroxide (1 N, 0·08 ml) were left at room temp overnight. The solution (pH 7·5) was then acidified with sulphuric acid (10 N, 0·15 ml) and heated in a sealed tube at 110° for 2 hr. After extraction of iodine with carbon tetrachloride, followed by neutralization with barium carbonate and centrifugation, a clear solution was obtained. Paper chromatography with solvent (a) showed only a single spot of reducing sugar, corresponding to galactose, but with solvent (b) the formation of gluconic acid was clearly indicated.

*Methylation.* The trisaccharide (1·5 g) was methylated twice with methyl sulphate and twice with Purdie's reagents, according to Kuhn *et al.*,[14] except that after the second treatment with methyl sulphate the mixture was kept 4 hr. at 40–50°. The final product was a non-reducing syrup.

*Hydrolysis and fractionation of methylated galactosyl-lactose.* The syrup (0·37 g) was hydrolyzed according to Whistler and Conrad[18] and the hydrolysates were fractionated on a column of charcoal-celite, using for elution a linear gradient of ethyl methyl ketone between 2·5 and 10% concentration in water.[5] Three well separated peaks were obtained (Fig. 1), each of them containing a single substance, as shown by paper chromatography with solvents (c), (d) and (e). Comparison with authentic specimens of methylated hexoses indicated that the first peak contained 2,3,4-tri-O-methyl-D-galactose, the second 2,3,6-tri-O-methyl-D-glucose and the third 2,3,4,6-tetra-O-methyl-D-galactose (Table 2).

[16] N. Nelson, *J. Biol. Chem.* **153**, 375 (1944).
[17] H. Bouveng and B. Lindberg, *Acta Chem. Scand.* **10**, 1515 (1956).
[18] R. L. Whistler and H. E. Conrad, *J. Amer. Chem. Soc.* **76**, 1673 (1954).

TABLE 1. COMPARISON OF THE PAPER CHROMATOGRAPHIC MOBILITIES ($R_L$)* OF DISACCHARIDES OBTAINED BY THE PARTIAL HYDROLYSIS OF GALACTOSYL-LACTOSE WITH THOSE OF 6-O-β-D-GALACTOPYRANOSYL-D-GALACTOSE AND OF LACTOSE

| Compound | Solvent (a) | Solvent (d) |
|---|---|---|
| Disaccharides from partial hydrolysis of galactosyl-lactose | 0·68, 1·00 | 0·72, 1·00 |
| 6-O-β-D-galactopyranosyl-D-galactose | 0·68 | 0·72 |
| Lactose | 1·00 | 1·00 |

* Ratio of the distance moved by each substance to that moved by lactose.

TABLE 2. COMPARISON OF THE PAPER CHROMATOGRAPHIC MOBILITIES ($R_g$) OF SOME AUTHENTIC METHYLATED HEXOSES WITH THOSE OF THE SUGARS OBTAINED BY THE FRACTIONATION OF AN ACID HYDROLYSATE OF FULLY METHYLATED GALACTOSYL-LACTOSE, ON A CHARCOAL–CELITE COLUMN

| Compound | Solvent (a) | Solvent (d) | Solvent (e) |
|---|---|---|---|
| Sugar from first peak | 0·71 | 0·62 | 0·58 |
| 2,3,4-tri-O-methyl-D-galactose | 0·71 | 0·61 | 0.58 |
| Sugar from second peak | 0·78 | 0·69 | 0·70 |
| 2,3,6-tri-O-methyl-D-glucose | 0·80 | 0·70 | 0·72 |
| Sugar from third peak | 0·84 | 0·74 | 0·78 |
| 2,3,4,6-tetra-O-methyl-D-galactose | 0·84 | 0·73 | 0·77 |

This was confirmed as follows. Material obtained from the first peak, after evaporation to dryness *in vacuo*, had $[\alpha]_D^{27}$ +111° (*c*, 0·2 in $H_2O$) and when refluxed with ethanolic aniline for 5 hr gave 2,3,4-tri-O-methyl-N-phenyl-D-galactosylamine m.p. 163° which was not depressed on admixture with an authentic sample supplied by Dr. B. Lindberg. Furthermore, on oxidation with periodate the peak material yielded formaldehyde (identified colorimetrically with chromotropic acid). The residue obtained on evaporation of the second peak had $[\alpha]_D^{25}$ +70° (*c*, 0·3 in $H_2O$) and showed a very remarkable drop in optical rotation when a 1% solution in 2% methanolic hydrogen chloride was kept at room temp. The syrup obtained by concentration of the third peak had $[\alpha]_D^{25}$ +115° (*c*, 0·43 in $H_2O$) and gave an aniline derivative, m.p. 187° which was not depressed on admixture with a sample of 2,3,4,6-tetra-O-methyl-N-phenyl-D-galactosylamine obtained through the courtesy of Dr. P. W. Kent.

The approximate molar ratios of the three methylated sugars were determined by optical rotation measurements on the individual peaks obtained from the column. Figures close to 1 : 1 : 1 were obtained when $[\alpha]_D$ values recorded in the literature for 2,3,4-tri-O-methyl-D-galactose, 2,3,6-tri-O-methyl-D-glucose and 2,3,4,6-tetra-O-methyl-D-galactose were used.

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# THE CHEMISTRY OF YLIDS—V

## TRIALKYLPHOSPHONIUMFLUORENYLIDES MECHANISM OF THE WITTIG REACTION[1]

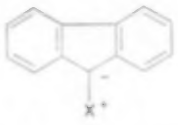
A. WM. JOHNSON and R. B. LACOUNT
Mellon Institute, Pittsburgh 13, Pennsylvania

(*Received* 9 *November* 1959)

**Abstract**—Trimethyl- and tri-n-butylphosphoniumfluorenylide (Ib and Id respectively) have been prepared and their relative reactivities in the Wittig reaction have been established. The various factors which control the success or failure of this reaction have been elucidated. A means of predicting the reactivity of ylids has been established.

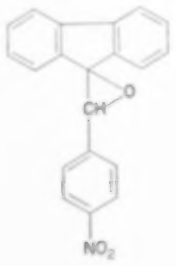
### INTRODUCTION

IN an earlier communication[2] we reported on the reaction between dimethylsulfonium-

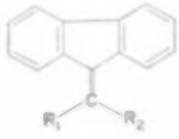


Ia X = $(CH_3)_2S$
b $(CH_3)_3P$
c $(C_6H_5)_3P$
d $(n\text{-}C_4H_9)_3P$
e $(C_6H_5)_3As$

fluorenylide (Ia) and *p*-nitrobenzaldehyde which afforded mainly *p*-nitrobenzalfluorene oxide (II). This was a somewhat surprising result, our earlier expectation being the formation of *p*-nitrobenzafluorene (IIIa) by analogy with the reactions of triphenylphosphoniumfluorenylide (Ic).[3] In spite of the ease of accounting for the result



II



III a $R_1$ = H $R_2$ = $C_6H_4$—$NO_2$(*p*)
b $R_1$ = H $R_2$ = $C_6H_5$
c $R_1$ = H $R_2$ = $C_6H_4$—$OCH_3$(*p*)

mechanistically our curiosity was roused as to the reasons for this change in mechanism. Since at that time no trialkylphosphonium ylid (e.g. IV) had been reported to undergo a normal Wittig reaction, it was initially suspected that the use of an *alkyl* ylid in place of an *aryl* ylid was responsible for the mechanistic change observed in the sulphur case. We therefore undertook to examine the chemistry of a trialkylphosphoniumfluorenylide and compare the results with those of Ia.

[1] For the previous paper in this series see A. W. Johnson, *J. Org. Chem.* In press.
[2] A. W. Johnson and R. B. LaCount, *Chem. & Ind.* 1440 (1958).
[3] A. W. Johnson, *J. Org. Chem.* **24**, 282 (1959).

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Only two trialkylphosphonium ylids have been reported to date. Wittig and Laib[4] prepared ethereal solutions of trimethylphosphoniumfluorenylide (Ib) but reported no reactions with carbonyl compounds. However, Wittig and Rieber[5] reacted solutions of trimethylphosphoniummethylide (IV) with benzophenone and isolated, rather than the expected 1,1-diphenylethylene, a low yield of impure (2,2-diphenyl-2-hydroxyethyl) trimethylphosphonium iodide (V) after quenching with acid and potassium iodide. This product is the result of simple carbanion addition of the ylid across the carbonyl group.

$$(CH_3)_3P{=}CH_2 + (C_6H_5)_2CO \xrightarrow[KI]{H^+} (CH_3)_3\overset{+}{P}-CH_2-C(C_6H_5)_2\,Br^-\,I^-$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH$$

IV V

Wittig[6] and Levisalles[7] attributed the course of this reaction to the failure of the initially-formed betaine (e.g. VIIa, R″ = alkyl) to cyclize to a pentacolvalent intermediate (VIIb) due to the inductive effect of the alkyl groups hindering the attack of the oxyanion on phosphorus.

## RESULTS

Trimethylfluorenylphosphonium bromide was prepared from 9-bromofluorene and trimethylphosphine according to the procedure of Wittig and Laib.[4] An aqueous solution of this salt, when treated with sodium hydroxide solution, afforded a transitory yellow precipitate (Ib) which immediately hydrolyzed to fluorene and trimethylphosphine oxide. Benzene solutions of the ylid (Ib), prepared by treating the salt with phenyllithium, were reacted with several benzaldehydes to afford the corresponding benzalfluorenes (III). (See Table 1.)

TABLE 1. REACTION OF YLID Ib WITH CARBONYLS

| Carbonyl | Product | Yield |
|---|---|---|
| benzaldehyde | IIIb | 75% |
| *p*-nitrobenzaldehyde | IIIa | 74 |
| *p*-anisaldehyde | IIIc | 73 |

These results indicated that trimethylphosphonium ylids would undergo a normal Wittig reaction. However, it was apparent that they had lost the selectivity of reaction with benzaldehydes that was so apparent in the case of triphenylphosphonium-fluorenylide (Ic).[3] The latter reacted with the three benzaldehydes in 84, 96 and 37 per cent yields respectively. In order to explore further this difference and to obtain more accurate data it was deemed advisable to utilize a stable and isolable trialkyl-phosphonium ylid if available.

Accordingly, tri-n-butylphosphine was quaternized with 9-bromofluorene to afford tri-n-butylfluorenylphosphonium bromide which was in turn treated with sodium hydroxide solution to afford a stable, crystalline yellow ylid, tri-n-butylphosphonium-

[4] G. Wittig and H. Laib, *Liebigs Ann.* **580**, 57 (1953).
[5] G. Wittig and M. Rieber, *Liebigs Ann.* **562**, 177 (1949).
[6] G. Wittig and U. Schollkopf, *Chem. Ber.* **87**, 1318 (1954).
[7] J. Levisalles, *Bull. Soc. Chim.* 1021 (1958).

fluorenylide (Id). The ylid dissolved in dilute acids forming a colorless solution from which it could be reprecipitated unchanged by the addition of aqueous sodium hydroxide. The ultraviolet spectrum of Id in chloroform solution resembled that of Ic. The ylid was hydrolyzed to fluorene and tri-n-butylphosphine oxide by warming as an aqueous slurry but could be stored unchanged in a dessicator for one week. On attempting to pass a solution of the ylid through a column of nearly neutral alumina, equimolar quantities of fluorene and fluorenone together with a molar equivalent of tri-n-butylphosphine oxide were recovered. It appeared likely that the alumina

Table 2. Reaction of ylids with carbonyls

| Carbonyl | Yield of Olefin(III) with | |
|---|---|---|
| | *Ylid Ic** | *Ylid Id** |
| *Group A* ( 3 hr reaction) | | |
| Acetaldehyde | 90% | 93% |
| Acetone | 0† | 0† |
| *Group B* (3 hr reaction) | | |
| *p*-Nitrobenzaldehyde | 96 | 99 |
| *p*-Chlorobenzaldehyde | 93 | 96 |
| Benzaldehyde | 84 | 96 |
| *p*-Anisaldehyde | 37 | 94 |
| *p*-Dimethylaminobenzaldehyde | 0 | 94 |
| *Group C* (24 hr reaction) | | |
| *p, p'*-Dinitrobenzophenone | 0 | 93‡ |
| *p*-Nitrobenzophenone | — | 4 |
| Benzophenone | 0 | 0 |
| *Group D* (24 hr reaction) | | |
| *m*-Nitroacetophenone | — | 67 |
| *p*-Nitroacetophenone | — | 60 |
| *p*-Chloroacetophenone | — | 9 |
| Acetophenone | — | 0 |

* Yield based on total ylid added.
† Same yield after 24 hr reaction.
‡ Yield 15% after 3 hr reaction.

hydrolyzed some of the ylid in the normal fashion to fluorene and the phosphine oxide but the rest was probably cleaved to fluorenol and tri-n-butylphosphine. The latter would be immediately air oxidized[8] to its oxide while the fluorenol was likely oxidized by alumina to fluorenone since it was found that authentic fluorenol was slowly converted into fluorenone by an alumina column.

The ylid (Id) was reacted with a series of carbonyl compounds under standardized conditions in order to ascertain its reactivity. The results are recorded in Table 2. For comparison, the yields obtained with triphenylphosphoniumfluorenylide (Ic)[3] under identical conditions are also included.

Inspection of these results reveals that tri-n-butylphosphoniumfluorenylide (Id) is more reactive than its triphenyl analog (Ic). The latter exhibited selective reactivity with the group B carbonyls since substitution by a group (e.g. nitro) which increased the polarization of the benzaldehyde carbonyl group facilitated the reaction and vice

[8] G. M. Kosolapoff, *Organophosphorus Compounds* p. 23. John Wiley, New York (1950).

versa.[3] Tri-n-butylphosphoniumfluorenylide (Id) reacted equally well with all substituted benzaldehydes (group B) but did show selectivity in reaction with a series of less polarized carbonyls in groups C and D.

The p*K*a's of the conjugate acids of several fluorenyl ylids were measured spectrophotometrically and the results are listed in Table 3.

TABLE 3. p*K*a OF FLUORENYL YLID CONJUGATE ACIDS

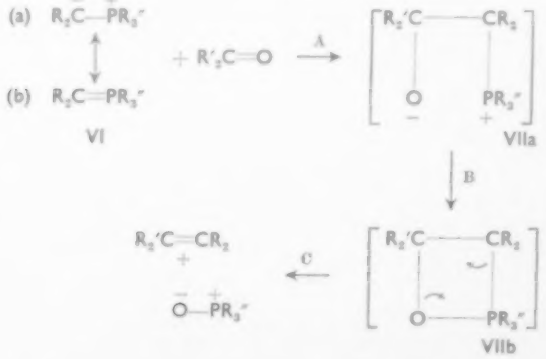
| Fluorenylide | p*K*a |
|---|---|
| Triphenylphosphonium | 7·5 |
| Triphenylarsonium | 7·8 |
| Tri-n-butylphosphonium | 8·0 |
| Dimethylsulfonium | 7·3 |

In an attempt to isolate a product analogous to Wittig's intermediate (V) acetone, *m*-nitroacetophenone and benzaldehyde, three carbonyl compounds of widely varying reactivity (see Table 2), were treated with equimolar quantities of the butyl ylid (Id) and the reactions were interrupted by the addition of gaseous hydrogen bromide. In the first instance 77 per cent of tri-n-butylfluorenylphosphonium bromide was recovered while in the third case only the expected olefin, benzalfluorene, was isolated. The *m*-nitroacetophenone reaction afforded a mixture of 14 per cent of the expected olefin product and 76 per cent of tri-n-butylfluorenylphosphonium bromide.

## DISCUSSION

The claim that trimethylphosphonium ylids should fail to undergo a complete and normal Wittig reaction[6,7] has been repudiated by the successful reactions reported in Tables 1 and 2. In fact, trialkyl ylids have been shown to be more reactive than the corresponding triphenyl ylids. This result was not unexpected as shown by the ensuing discussion. Under no circumstances could any intermediate be isolated, interception of the reactions affording only starting materials or the expected olefin products.

CHART 1



As is apparent from the currently accepted mechanism[9] reproduced in Chart I, several factors may control the success or failure of the three steps in the Wittig reaction.

Step A, involving the attack of an anionic centre at a carbonyl carbon, must be controlled in part by the polarity of the carbonyl group. That the reaction is facilitated by a highly polarized carbonyl group was demonstrated in the reaction of triphenylphosphoniumfluorenylide with substituted benzaldehydes[3] and is apparent from the reactivity of Id with less polar carbonyl compounds.

The carbanion character of the attacking ylid (VI) should also affect step A. Tending to decrease this character and hence the ease of attack at the carbonyl group will be resonance interactions (p–p$\pi$) with groups attached to the carbanion which tend to delocalize the negative charge (for example, VI, R = phenyl). The reality of this effect is evidenced by comparing triphenylphosphoniummethylide (VI, R = H, R″ = phenyl), which reacts with all aldehydes and ketones,[7] with triphenylphosphoniumcyclopentadienylide (VI, $R_2C$ = cyclopentadienyl, R″ = phenyl) which has been reported not to react with carbonyl compounds.[10] Triphenylphosphoniumfluorenylide (Ic) exhibited reactivity intermediate between these ylids.[3] These results verify that groups attached to the carbanion will decrease the reactivity of the ylid in proportion to their electron-withdrawing power.

The extent of (2p–3d) d-orbital resonance (i.e. the contribution of structure VIb to the resonance hybrid) between the carbanion and the phosphorus atom should also affect the carbanion character of VI. The less the contribution of form VIb to the resonance hybrid the greater should be the reactivity of the ylid. The degree of d-orbital resonance hinges upon a large formal positive charge on the phosphorus atom[11] and it is apparent that substituents (R″ in VI) can therefore affect the extent of this resonance through electronic interaction with the phosphorus atom. Jaffe,[12] Rao *et al.*[13a] and Mann[13b] have shown that there are no resonance interactions between benzenoid rings and tetracovalent phosphorus atoms. As a result, any interaction affecting the degree of positive charge on phosphorus must be of the inductive type. It is to be expected that the larger the —I (electron-withdrawing) effect of the phosphorus substituents the greater should be the operation of d-orbital resonance in the ylid.

This expectation is verified by four illustrations from the literature. Chatt *et al.*[14] recently reported that in planar complexes of the type trans-(L, piperidine $PtCl_2$), a larger ligand field splitting (a measure of the extent of d-orbital resonance between the metal atom and phosphorus) is shown for L = $P(OCH_3)_3$ than for L = $P(CH_3)_3$, as is expected only on the basis of a larger —I effect for the methoxyl group. Earlier, Chatt and Williams[15] showed, via the "trans effect," that the $\pi$-bonding ability of trivalent phosphorus decreased in the order $PF_3 > PCl_3 > P(OCH_3)_3 > P(CH_3)_3$, the same as the order of decreasing inductive electron-withdrawing(—I) effect of the substituents.

[9a] G. Wittig, *Angew. Chem.* **68**, 505 (1956); [9b] D. B. Denney and M. J. Boskin, *Chem. & Ind.* 330 (1959).
[10] F. Ramirez and S. Levy, *J. Amer. Chem. Soc.* **79**, 67 (1957).
[11] H. H. Jaffe, *J. Phys. Chem.* **58**, 185 (1954).
[12a] H. H. Jaffe, *J. Chem. Phys.* **22**, 1430 (1954).
[12b] H. H. Jaffe and L. D. Freedman, *J. Amer. Chem. Soc.* **74**, 1069 (1952).
[13a] C. N. R. Rao, J. Ramachandran, M. S. C. Iah, S. Somasekhara, T. V. Rajakumar, *Nature, Lond.* **183**, 1475 (1959).
[13b] F. G. Mann and E. J. Chaplin, *J. Chem. Soc.* 527 (1937).
[14] J. Chatt, G. A. Gamlen and L. E. Orgel, *J. Chem. Soc.* 1047 (1959).
[15] J. Chatt and A. A. Williams, *J. Chem. Soc.* 3061 (1951).

More recently, Meriwether and Fiene,[16a] via infrared spectra studies on nickeldicarbonyldiphosphines, elucidated the order $PCl_3 > P(OEt)_3 > P(C_6H_5)_3 > P(C_4H_9)_3$ for decreasing participation in d-orbital resonance. Similar conclusions have been reached by Wilkinson *et al.*[16b] from an examination of the infrared spectra of compounds of type $L_3Mo(CO)_3$ where L = ligand group.

Phenyl substituents in phosphonium ylids (VI, R″ = phenyl) would be expected to increase the formal positive charge on phosphorous via a —I effect[17] and therefore permit a larger contribution of form VIb to the resonance hybrid. On the other hand, alkyl substituents would be expected to decrease the contribution of form VIb via a +I effect. As a result trialkylphosphonium ylids (Ib, Id) would be expected to be more reactive than triphenylphosphonium ylids (Ic) and therefore undertake step A with greater ease. An examination of the results in Tables 1 and 2 verifies this hypothesis.

Additional evidence bearing on this expectation is provided by an examination of the p*K*a's of the conjugate acids of several onium fluorenylides reported in Table 3. It is to be expected that the greater the contribution of form VIb (via d-orbital resonance) to the resonance hybrid the more acidic will be the conjugate acid. Therefore, the more acidic conjugate acid should afford the least reactive ylid. This is in fact the case as the acidity of the fluorenylide conjugate acids decreases in the order dimethylsulfonium(Ia) > triphenylphosphonium(Ic) > triphenylarsonium(Ie) > tri-n-butylphosphonium (Id) but the reactivity decreases in the opposite order.[18] Hence, a measurement of the p*K*a value allows a prediction of the expected reactivity of an ylid.

The higher stability of the triphenylphosphonium ylid (Ic) compared to that of the trialkylphosphonium ylids (Ib, Id) toward hydrolysis is also consistent with a higher degree of d-orbital resonance in the former.

The factors affecting the facility with which step B occurs have not been elucidated. Levisalles[7] and Wittig[6] rationalized the reported failure of trimethylphosphonium ylids to undergo a Wittig reaction by failure of VIIa (R″ = alkyl) to form a pentacovalent intermediate (VIIb) via step B due to the electron-donating inductive effect of alkyl groups inhibiting the attack of the oxyanion on phosphorus. This effect is apparently non-existent in the cases we have examined. In view of the recent report[19] on the kinetics of the reaction of quaternary phosphonium salts with hydroxide ion in which the first step (fast) was the attack of hydroxide ion on the salt to form a pentacovalent intermediate (VIII) it is unlikely that the similar conversion of VIIa into VIIb (step B) controls the success of the Wittig reaction, regardless of the nature of the phosphorus substituents. (i.e., alkyl vs phenyl).

Little is known regarding the factors affecting step C of the Wittig reaction. This step is, however, similar to the slow step of the hydroxide decomposition of phosphonium salts[19] in which the pentacovalent intermediate (VIII) undergoes an electron

$$HO^- + \overset{+}{P}R_4 \xrightarrow{\text{fast}} [HO - PR_4] \xrightarrow[OX^-]{\text{slow}} H_2O + \overset{-}{O} - \overset{+}{P}R_3 + R^-$$

VIII

shift and loss of a hydrocarbon group with its electrons. The ease of departure of the

[16a] L. Meriwether and M. L. Fiene, *J. Amer. Chem. Soc.* **81**, 4200 (1959).
[16b] E. W. Abel, M. A. Bennett and G. Wilkinson, *J. Chem. Soc.* 2323 (1959).
[17] B. M. Wepster, *Rec. Trav. Chim.* **71**, 1171 (1952).
[18] The reactivity data for Ic and Id are reported in this paper and that for Ie is reported in ref. 1. The data for Ia is not yet published.
[19] M. Zanger, C. A. VanderWerf and W. E. McEwen, *J. Amer. Chem. Soc.* **81**, 3806 (1959).

hydrocarbon group paralleled its stability as an anion. The same electron shift takes place in step C of the Wittig reaction and if the same effect is operative (i.e., the electron-withdrawing ability of the group $CR_2$) and controls the decomposition of VIIb, two intermediates differing only in the nature of the group R″ should decompose at nearly the same rate. That this is *not* the case is apparent from the difference in the reaction of the ylids Ic and Id with, for example, *p*-dimethylaminobenzaldehyde (see Table 2).

It is apparent that the course of the Wittig reaction and the relative ease with which various ylids and carbonyl compounds partake in it can best be accounted for on the basis of the initial condensation (step A) controlling the fate of the reaction. Steric effects, if of major importance, may result in step B becoming rate-controlling. However, in all cases studied herein and, to our knowledge, all examples reported to date steric effects are not important. Doubtless a specially designed example in which it is sterically impossible or highly unfavorable to bring the phosphonium and oxyanion groups together could be found and would permit isolation of an intermediate (VIIa). Hence, the Wittig reaction will probably evolve as another case where either electrical or steric effects may be of major importance, depending on the particular reactants involved.

## CONCLUSIONS

1. Trialkyl ylids are more reactive than triphenyl ylids.

2. The initial step (A) in the condensation of an ylid with a carbonyl compound controls the success or failure of the Wittig reaction.

3. An estimate of the reactivity of an ylid may be obtained by a measure of the p*K*a of its conjugate acid. A theoretical prediction of the reactivity of an ylid may be made by considering its carbanion character as influenced by p- and d-orbital resonance.

## EXPERIMENTAL[20]

*Trimethylphosphoniumfluorenylide* (Ib). Trimethylfluorenylphosphonium bromide was prepared from trimethylphosphine and 9-bromofluorene[21] in 57% yield according to the procedure of Wittig and Laib.[4] It crystallized from benzene–ethanol as colorless needles, m.p. 221–223° (Lit.,[4] m.p. 218–219°). (Found: C, 59·6; H, 5·6; P, 9·7; Br, 25·0 Calc. for $C_{16}H_{18}PBr$: C, 59·9; H, 5·6; P, 9·7; Br, 24·9%).

A small sample of the salt was dissolved in water and treated with a few drops of sodium hydroxide solution. A yellow precipitate formed immediately which faded to a colorless precipitate. The latter was filtered and dried to m.p. 112–114°, undepressed on admixture with authentic fluorene.

To a stirred slurry of 3·0 g (9·36 mmoles) of the salt in 75 ml benzene covered with an atmosphere of nitrogen was added 24·4 ml 0·4 molar phenyllithium solution. The colorless suspension, on heating under reflux for 6 hr, gradually formed a yellow solution of *trimethylphosphoniumfluorenylide* (Ib).

*Reaction of trimethylphosphoniumfluorenylide* (Ib) *with carbonyls*

To solutions of 3·13 mmoles of the benzaldehydes in 25 ml benzene was added a benzene solution of 3·13 mmoles of ylid (Ib). The resulting mixtures were heated under reflux for 3 hr, then cooled, any solids removed by filtration and the filtrates evaporated. The residues were crystallized in each case.

Benzaldehyde afforded 0·55 g (75%) *benzalfluorene* (IIIb) which crystallized from ethanol–water as colorless plates, m.p. 74–76°, undepressed on admixture with an authentic sample. (Lit.,[3] m.p. 75–76°).

*p*-Nitrobenzaldehyde afforded 0·70 g (74%) p-*nitrobenzalfluorene* (IIIa) which crystallized from ethanol as yellow needles, m.p. 165–167°, undepressed on admixture with an authentic sample. (Lit.[3] m.p. 167–168°).

[20] Melting points are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratories, Woodside 77, NY. Ultraviolet spectra were recorded on a Cary model 14 spectrophotometer.

[21] G. Wittig and G. Felletschin, *Liebigs Ann.* **555**, 133 (1944).

*p*-Anisaldehyde afforded 0·67 g (73%) p-*anisalfluorene* (IIIc) which crystallized from ethanol as pale yellow plates, m.p. 129·5–130·5°, undepressed on admixture with an authentic sample. (Lit.,[3] m.p. 130–131°).

*Tri-n-butylphosphoniumfluorenylide* (Id). To a solution of 11 g (0·045 mmole) 9-bromofluorene[21] in 75 ml acetone covered with an atmosphere of nitrogen was added 9·2 g (0·045 mmole) tri-n-butylphosphine[22] forming a copious precipitate. The latter (9·4 g, 47%) was filtered after standing several hours. Recrystallization from ether–ethanol afforded *tri-n-butylfluorenylphosphonium bromide* as colorless microcrystals, m.p. 194–195°. (Found: C, 67·2; H, 8·2; P, 7·1; Br, 18·3 $C_{25}H_{36}PBr$ requires: C, 67·1; H, 8·1; P, 6·9; Br, 17·9%). An aqueous solution of the salt gave a positive silver nitrate test for ionic halogen and afforded a yellow precipitate when treated with ammonia or sodium hydroxide solutions. The salt was not converted into fluorenol and tri-n-butylphosphine upon warming in water, but was recovered unchanged.

To an aqueous solution of 16 g (0·036 mole) of the salt was added several ml 1·0 N sodium hydroxide solution until precipitation of the yellow ylid was complete. The ylid was filtered and washed with water and ether. Recrystallization from ether afforded 7·6 g (66%) *tri-n-butylphosphoniumfluorenylide* (Id) as yellow microcrystals, m.p. 123–124°. (Found: C, 82·1; H, 9·6; P, 8·2. $C_{25}H_{35}P$ requires: C, 82·2; H, 9·4; P, 8·5%). The ylid dissolved in dilute mineral acid and was reprecipitated unchanged upon basification. Ultraviolet spectrum (chloroform): $\lambda_{max}$(Log $\varepsilon$) 250 m$\mu$ (4·8), 258 (5·0), 284 (3·6), 295 (3·6), 308 (3·3), 325 (3·0), 379 (2·5).

To a solution of 0·5 g sodium hydroxide in 20 ml methanol was added 0·3 g ylid (Id) and the slurry was heated under reflux for 5 hr. Upon quenching with water the solution afforded a colorless precipitate (0·13 g, 98%) which crystallized from ethanol as colorless plates, m.p. 111–113°, undepressed on admixture with authentic fluorene. The ylid afforded no fluorene upon standing for 5 hr as an aqueous slurry.

A benzene solution of 300 mg ylid (Id) was passed onto a column of 10 g Merck No. 71707 alumina. Eluted, in the following order, were 60 mg (44%) of fluorene, m.p. 110–111°, undepressed on admixture with an authentic sample, 70 mg (48%) fluorenone, m.p. 81–83°, undepressed on admixture with an authentic sample and 170 mg (95%) tri-n-butylphosphine oxide, identified by a comparison of its infrared spectrum with that of an authentic sample.

Passage of a solution of 200 mg 9-fluorenol through a column of 10 g Merck No. 71707 alumina afforded 55 mg fluorenone, m.p. 84–85°, identified via its infrared spectrum and admixture melting point.

*Condensation of tri-n-butylphosphoniumfluorenylide* (Id) *with carbonyls*

A standard procedure was used in all reactions. To a solution of 1·0 g (2·74 mmoles) ylid (Id) in 25 ml dry benzene was added 2·74 mmoles of the appropriate carbonyl compound and the solution was heated under reflux for 3 hr. In cases where there was little or no reaction after this time, the reaction was allowed to proceed for 24 hr. The benzene was evaporated on the steam bath and 15 ml hot ethanol was added to the residue. Any unchanged ylid was removed via filtration and the product was then precipitated by the addition of water and recrystallized. The pertinent data is recorded in Table 4. The yield of olefin does not take into account any recovered ylid. The products were identified, in all cases except those of new compounds whose analyses are listed below, by comparison with literature data and by admixture melting points with authentic samples. The following analyses were found for the new compounds.

*ω-Phenyl-ω-(p-nitrophenyl)dibenzofulvene.* (Found: C, 82·7; H, 4·7; N, 3·5. $C_{25}H_{17}NO_2$ requires: C, 83·2; H, 4·6; N, 3·7%).

*ω,ω-bis(p-nitrophenyl)dibenzofulvene.* (Found: C, 73·9; H, 4·2; N, 6·8. $C_{26}H_{16}N_2O_4$ requires: C, 74.3; H, 3·8; N, 6·7%).

*ω-Methyl-ω-(p-nitrophenyl)dibenzofulvene.* (Found: C, 80·6; H, 4·9; N, 4·5. $C_{21}H_{15}NO_2$ requires: C, 80·5; H, 4·8; N, 4·5%).

*ω-Methyl-ω-(m-nitrophenyl)dibenzofulvene.* (Found: C, 80·0; H, 5·2; N, 4·9. $C_{21}H_{15}NO_2$ requires: C, 80·5; H, 4·8; N, 4·5%).

*ω-Methyl-ω-(p-chlorophenyl)dibenzofulvene.* (Found: C, 83·4; H, 5·2; Cl, 11·4. $C_{21}H_{15}Cl$ requires: C, 83·3; H, 5·0; Cl, 11·7%).

[1] We thank Metal and Thermit Corp., Rahway, N.J., for a generous sample of tri-n-butylphosphin

*Acidity of ylid conjugate acids.* The p*K*a's were determined by direct spectrophotometric measurement of the ratio of acidic and basic forms in a buffer solution.[23] The ultraviolet spectra were recorded of $10^{-4}$ molar solutions of the hydrobromides of the ylids Ia, Ic, Id and Ie (listed in Table 3) each in 0·1 N sodium hydroxide, 0·1 N hydrochloric acid and acetate buffer (pH 5·86) solutions. The solvent in each case was 31.7% water–dioxane. The values reported in Table 3 are the average of at least three determinations.

TABLE 4. REACTION OF YLID (Id) WITH CARBONYLS

| Carbonyl | Expected product (III) | | Time (hr.) | Yield of III | M.P. | Lit. M.P. (Ref.) | Recovered ylid |
|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | | | | | |
| Acetaldehyde | H | $CH_3$ | 3 | 93% | 102–104 | 102–104[1] | 0% |
| Acetone | $CH_3$ | $CH_3$ | 3<br>24 | 0<br>0 | —<br>— | —<br>— | 94<br>94 |
| *p*-Nitrobenzaldehyde | H | $C_6H_4NO_2(p)$ | 3 | 99 | 167–168 | 167–168[a] | 0 |
| *p*-Chlorobenzaldehyde | H | $C_6H_4Cl(p)$ | 3 | 96 | 149–150 | 147–148[1] | 0 |
| Benzaldehyde | H | $C_6H_5$ | 3 | 96 | 72–73 | 75–76[a] | 0 |
| *p*-Methoxybenzaldehyde | H | $C_6H_4OCH_3(p)$ | 3 | 94 | 128–129 | 130–131[a] | 0 |
| *p*-Dimethylamino-benzaldehyde | H | $C_6H_4N(CH_3)_2(p)$ | 3 | 94 | 135–136 | 135–136[1] | 0 |
| *p,p'*-Dinitrobenzophenone | $C_6H_4NO_2$(p) | $C_6H_4NO_2(p)$ | 3<br>24 | 15<br>93 | 266–267 | — | 53<br>0 |
| *p*-Nitrobenzophenone | $C_6H_5$ | $C_6H_4NO_2(p)$ | 24 | 4 | 186–187 | — | 67 |
| Benzophenone | $C_6H_5$ | $C_6H_5$ | 24 | 0 | — | — | 93 |
| *m*-Nitroacetophenone | $CH_3$ | $C_6H_4NO_2(m)$ | 24 | 67 | 152–153 | — | 31 |
| *p*-Nitroacetophenone | $CH_3$ | $C_6H_4NO_2(p)$ | 24 | 60 | 154–155 | — | 0 |
| *p*-Chloroacetophenone | $CH_3$ | $C_6H_4Cl(p)$ | 24 | 9 | 149–150 | — | 28 |
| Acetophenone | $CH_3$ | $C_6H_5$ | 24 | 0 | — | — | 93 |

*Condensation of* Id *with acetone.* A solution of 0·3 g (0·82 mmole) ylid (Id) and 0·1 g (1·7 mmoles) acetone in 25 ml benzene was heated under reflux for 3 hr after which anhydrous hydrogen bromide was passed through the solution. The benzene was evaporated, the oily residue extracted with water and the latter concentrated to afford 0·28 g (77%) of a colorless solid, m.p. 191–193°, undepressed on admixture with authentic tri-n-butylfluorenylphosphonium bromide.

*Condensation of* Id *with benzaldehyde.* A solution of 0·5 g (1·37 mmoles) ylid (Id) and 0·15 g (1·37 mmoles) benzaldehyde in 25 ml benzene was heated under reflux for ½ hr after which anhydrous hydrogen bromide was passed into the solution. The benzene was evaporated and the residue extracted with water and then with ether. Evaporation of the water afforded no unchanged salt. Evaporation of the ethereal extract afforded 0·27 g (78%) benzalfluorene, m.p. 73–75, undepressed on admixture with an authentic sample.

*Condensation of* Id *with* m*-nitroacetophenone.* A solution of 1·20 g (3·3 mmoles) ylid (Id) and 0·54 g (3·3 mmoles) *m*-nitroacetphenone in 25 ml benzene was heated under reflux for 4 hr after which anhydrous hydrogen bromide was passed through the solution. The same work-up as employed above afforded 1·11 g (76%) recovered tri-n-butylfluorenylphosphonium bromide and 0·14 g (14%) ω-methyl-ω-(*m*-nitrophenyl)dibenzofulvene, m.p. 153–154, undepressed on admixture with an authentic sample.

[23] L. A. Flexser, L. P. Hammett and A. Dingwall, *J. Amer. Chem. Soc.* **57**, 2103 (1935).

Tetrahedron, 1960, Vol. 9, pp. 139 to 144. Pergamon Press Ltd. Printed in Northern Ireland

# CONSTITUENTS OF *CASIMIROA EDULIS* LLAVE *ET* LEX.—VI[1]

## 2′,5,6-TRIMETHOXYFLAVONE, 2′,5,6,7-TETRAMETHOXYFLAVONE (ZAPOTIN) AND 5-HYDROXY-2′,6,7-TRIMETHOXYFLAVONE (ZAPOTININ)

F. SONDHEIMER and A. MEISELS
The Daniel Sieff Research Institute,
Weizmann Institute of Science, Rehovoth

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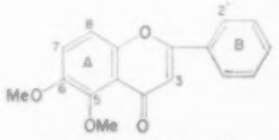
**Abstract**—Experiments are described which show that a substance isolated from the root bark of *Casimiroa edulis* Llave *et* Lex. is 2′,5,6-trimethoxyflavone (IIa). It is demonstrated that zapotin and zapotinin, isolated previously from the same plant, are very probably 2′,5,6,7-tetramethoxyflavone (IIIa) and 5-hydroxy-2′,6,7-trimethoxyflavone (IIIb), respectively. The occurrence in nature of flavonoids of type IIa, IIIa and IIIb bearing a single oxygen substituent in ring B at the 2′-position is unusual.

### 2′,5,6-*Trimethoxyflavone*

THE isolation[2,3] and structure elucidation[4] of the carbostyril alkaloid casimiroin, a constituent of the fruit and bark of the tree *Casimiroa edulis* Llave *et* Lex., has been described previously. Pure casimiroin had been obtained by our group[3] by careful chromatography on alumina followed by crystallization to constant melting point. We have now found that the mother liquors remaining after this crystallization contain another substance.

Indications of this second product were first obtained when it was found that impure casimiroin derived from the root bark[3b] on being boiled with 20 per cent hydrochloric acid yielded the colourless casimiroinol[2,3a] accompanied by a yellow impurity. Casimiroin mother liquors were therefore re-chromatographed on alumina, when the acompanying substance was obtained as colourless plates, m.p. 125°.

The empirical formula of this compound was found to be $C_{18}H_{16}O_5$ and it contained three methoxyl groups. The spectral data (multiple absorption in the 6·0–6·5 $\mu$ region




I

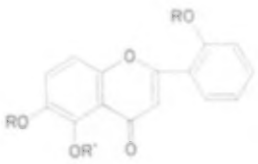
in the infra-red; ultra-violet maxima at 234, 268 and 328 m$\mu$) were quite similar to those of 5,6-dimethoxyflavone (I) already found[3b] in the bark of *Casimiroa edulis*. These facts strongly suggested a trimethoxy-flavone or -isoflavone structure.[5]

[1] Part V: F. Sondheimer, A. Meisels and F. A. Kincl, *J. Org. Chem.* **24**, 870 (1959).
[2] F. B. Power and T. Callan, *J. Chem. Soc.* **99**, 1993 (1911).
[3a] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956); [b] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *Ibid.* 4170 (1956).
[4] A. Meisels and F. Sondheimer, *J. Amer. Chem. Soc.* **79**, 6328 (1957).
[5] The ultra-violet spectrum does not allow a clear distinction to be made between these classes of compounds, as is evident from an inspection of the spectra of a variety of flavones[6a-12d] and isoflavones.[7]

The methoxyl groups could be cleaved by means of hydriodic acid in acetic anhydride, which yielded the corresponding yellow trihydroxy-compound, $C_{15}H_{10}O_5$, m.p. 280°, characterized as the triacetate, $C_{21}H_{16}O_8$, m.p. 142°. No rearrangement[8] had occurred in the demethylation reaction, since methylation of the product with methyl sulphate and potassium carbonate in acetone regenerated the starting material. Fusion of the trihydroxy-compound with potassium hydroxide at 210° yielded over 50 per cent of salicylic acid, but no other phenol except for a considerable amount of unchanged starting material could be isolated. The stability of the trihydroxy-compound to alkali is noteworthy and speaks against an isoflavone structure, since the latter class of compound is usually cleaved readily with base.[7,9] It appears therefore that the natural compound is a 2′-methoxyflavone or alternatively a flavone unsubstituted in ring A, either structure accounting for the formation of salicylic acid.

Boiling of the natural compound with 20 per cent hydrochloric acid resulted in the cleavage of only one methoxyl group and gave 80 per cent of a yellow dimethoxy-monohydroxy compound, m.p. 154°. This substance (which is the yellow impurity found in the conversion of crude casimiroin to casimiroinol, referred to above) was also obtained from the trihydroxy-compound by methylation with diazomethane. The ready demethylation of one methoxyl group and resistance to methylation of the corresponding hydroxyl group is typical of a substituent at the 5-position.[10a] That the hydroxyl group in the dimethoxy-hydroxy compound is at C-5 is confirmed by the fact that no hydroxyl band in the 3 $\mu$ region was apparent in its infra-red spectrum (due to chelation)[11] and that it gave a dark green colour with ferric chloride.[6b,12a] A ring A-unsubstituted structure is therefore excluded and two of the three methoxyl groups are at the 2′ and 5-positions. The third methoxyl group was tentatively placed at C-6 since the trihydroxy-compound gave a stable yellow-brown colour with sodium hydroxide, indicative of two vicinal hydroxyl groups.[12b]

Fortunately, 2′,5,6-trimethoxyflavone (IIa) has recently been synthesized by Doporto *et al.*[13] and the melting points reported for this substance as well as for the




IIa, R = R′ = Me
b, R = R′ = H
c, R = R′ = Ac
d, R = Me, R′ = H

[6] *Inter al.* [c] S. Aronoff, *J. Org. Chem.* **5**, 561 (1940); [b] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3136 (1951).
[7] *Inter al.* [a] W. K. Warburton, *Quart. Rev.* **8**, 67 (1954); [b] P. Crabbé, P. R. Leeming and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 5258 (1958); [c] L. H. Briggs and B. F. Cain, *Tetrahedron* **6**, 143 (1959).
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[9] A. Robertson, C. W. Suckling and W. B. Whalley, *J. Chem. Soc.* 1571 (1949); F. E. King, T. J. King and A. J. Warwick, *Ibid.* 96 (1952).
[10] S. Wawzonek, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 2; [a] p. 265; [b] p. 267; [c] p. 268. John Wiley, New York (1951).
[11] H. L. Hergert and E. F. Kurth, *J. Amer. Chem. Soc.* **75**, 1622 (1953); B. L. Shaw and T. H. Simpson, *J. Chem. Soc.* 655 (1955).
[12] T. A. Geissmann, *Modern Methods of Plant Analysis* (Edited by K. Paech and M. V. Tracey) [a] p. 467; [b] pp. 468–470; [c] pp. 471–472; [d] p. 487. Springer Verlag, Berlin (1955).
[13] M. L. Doporto, K. M. Gallagher, J. E. Gowan, A. C. Hughes, E. M. Philbin, T. Swain and T. S. Wheeler, *J. Chem. Soc.* 4249 (1955).

trihydroxy-compound IIb and the triacetate IIc agreed well with those of the corresponding compounds derived from *Casimiroa edulis*. Samples* of synthetic 2′,5,6-trimethoxyflavone (IIa) and 2′,5,6-trihydroxyflavone (IIb) were obtained and we prepared 5-hydroxy-2′,6-dimethoxyflavone (IId) from the latter by treatment with diazomethane. Direct comparison showed that the three synthetic substances were completely identical with the respective natural compounds, and our structural assignments are therefore correct.

*Zapotin* (2′,5,6,7-*tetramethoxyflavone*) *and zapotinin* (5-*hydroxy*-2′,6,7-*trimethoxy- flavone*)

We now turn to a consideration of the structures of zapotin and zapotinin, two further flavonoid constituents isolated from *Casimiroa edulis* Llave *et* Lex.[3] Zapotin, $C_{19}H_{18}O_6$, containing four methoxyl groups, was considered to be the tetramethyl ether of a tetrahydroxyflavone or isoflavone, although the exact structure was not elucidated.[3a] Zapotinin, $C_{18}H_{16}O_6$, containing three methoxyl and one hydroxyl group, was shown to be a corresponding trimethyl ether and it could be obtained from zapotin by fusion with potassium hydroxide at 270°.[3a]

Zapotin in its properties and reactions closely resembles the above-described 2′,5,6-trimethoxyflavone (IIa), including the infra-red and ultra-violet spectra.[3a] Boiling 20 per cent hydrochloric acid has now been found also to result in the cleavage of one methoxyl group to yield over 90 per cent of zapotinin.[14] Boiling hydriodic acid has been shown to convert zapotin to the corresponding tetrahydroxy-compound, demethylzapotin. Treatment of the latter substance with diazomethane leads to zapotinin, only three of the four hydroxyl groups being methylated.[3a] The fourth hydroxyl group is attacked when the methylation is carried out with methyl sulphate and potassium carbonate in acetone, the product being zapotin (see Experimental).

The stability of the ring system of zapotin and zapotinin to base again suggests a flavone rather than an isoflavone structure. The fact that one methoxyl group in zapotin is cleaved readily, while the corresponding hydroxyl group is methylated only with difficulty, is also indicative of a 5-methoxy structure.[10a] This is confirmed by the fact that zapotinin gives a dark green colour with ferric chloride[6b,12a] and in the infra-red does not show a hydroxyl band in the 3 $\mu$ region.[11]

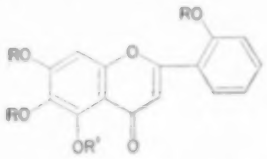
Alkali fusion of demethylzapotin had previously given salicylic acid in high yield.[3a] Since a 5-hydroxyl group is present, this acid must be derived from ring B and consequently zapotin appears to be a 2′,5-oxygenated flavone with no other substituents in ring B. The alkali fusion of demethylzapotin had also given resorcinol in low yield as the only phenol to be isolated, this compound probably being formed by secondary changes. Repeated attempts to isolate other phenols were unsuccessful and no structural information regarding the oxygenation pattern of ring A could be obtained by this means.

The positions which can be considered for the remaining two methoxyl groups in zapotin are the 3-, 6-, 7-, and 8-positions. A 3-methoxy structure can be excluded since demethylzapotin does not give a bright colour with magnesium and hydrochloric

* Kindly provided by Professor T. S. Wheeler and Dr. E. M. Philbin.

[14] Zapotin in benzene solution is unaffected on treatment with 4% hydrochloric acid at room temperature, the conditions under which it was isolated.[3] It therefore appears that zapotinin is not an artefact formed from zapotin during the isolation process, although this possibility cannot be excluded with complete certainty.

acid (Shinoda test for flavonols).[12c] The 8-position is also apparently unsubstituted since demethylzapotin gives no colour with *p*-benzoquinone (a 5,8-dihydroxyflavone would have been oxidized to a quinone under these conditions).[15] Zapotin therefore appears to be 2′,5,6,7-tetramethoxyflavone (IIIa) and zapotinin 5-hydroxy-2′,6,7-trimethoxyflavone (IIIb). In agreement with these formulations is the fact that demethylzapotin (IIIc) with sodium hydroxide undergoes a series of colour changes to




IIIa, R=R′=Me
b, R=Me, R′=H
c, R=R′=H

be expected if at least three hydroxyl groups are in adjacent positions [12b,16], and with sodium amalgam in ethanol it forms a green flocculent precipitate (this reaction, the Bargellini test, is indicative of a 5,6,7-trihydroxyflavone, although it does not definitely exclude certain other oxygenation patterns).[10c,17] The flavone structure is confirmed by the fact that zapotin and demethylzapotin show quite different physical properties from those of the recently described[7b] 2′,5,6,7-tetramethoxy- and 2′,5,6,7-tetrahydroxyisoflavone, respectively. There seems little doubt of the corrections of structure IIIa for zapotin and IIIb for zapotinin, and we hope to provide final proof through synthesis.

It is of interest to note from the biogenetic standpoint that 5,6-dimethoxyflavone (I), 2′,5,6-trimethoxyflavone (IIa) and 2′,5,6,7-tetramethoxyflavone (IIIa) occur together in the same plant. Of especial interest is the fact that 2′,5,6-trimethoxyflavone, zapotin and zapotinin appear to be the first examples of natural flavones (as opposed to flavonols) bearing a single oxygen substituent in ring *B* at the 2′-position. This substitution pattern in ring B is also quite rare in other naturally occurring flavonoids, only one example each in the flavonol,[18a] flavanone[18b] and isoflavone[18c] series being known.

## EXPERIMENTAL[19]

*Isolation of* 2′,5,6-*trimethoxyflavone* (IIa) *from crude casimiroin*

Crude casimiroin (4·2 g; m.p. 198–199°; derived from the root bark of *Casimiroa edulis* Llave *et* Lex.[20]) was crystallized from acetone–hexane. The dried mother liquors (1·0 g) were then chromatographed on 30 g alumina (Merck "acid-washed"). Benzene eluted 0·65 g 2′,5,6-trimethoxyflavone, m.p. 118–119°, which after crystallization from acetone formed colourless plates, m.p. 124–125° (reported:[12] m.p. 124–125°); infra-red bands at 6·06, 6·15 and 6·34 $\mu$; $\lambda_{max}$ 234, 268 and 328 m$\mu$ (log $\varepsilon$, 3·91, 4·02 and 3·88, respectively). An alcoholic solution with magnesium and hydrochloric acid gave an orange colour (3-methoxy group absent).[12c] (Found: C, 69·43; H, 4·93; $CH_3O$, 29·68. Calc. for $C_{18}H_{18}O_5$: C, 69·22; H, 5·16; 3 $CH_3O$, 29·78%).

[15] The gossypitone reaction; see footnote 10*b* and A. G. Perkin, *J. Chem. Soc.* **103**, 657 (1913).
[16] L. R. Row and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **22A**, 215 (1945).
[17] G. Bargellini, *Gazz. Chim. Ital.* **49**, II, 47 (1919); P. S. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **17A**, 119 (1943).
[18a] Datiscetin (2′,5,7-trihydroxyflavonol): J. Kalff and R. Robinson, *J. Chem. Soc.* 1968 (1925); [b] citronetin (5,7-dihydroxy-2′-methoxyflavanone): *inter al.* T. H. Simpson and W. B. Whalley, *Ibid.* 166 (1955); [c] tlatlancuayin (2′,5-dimethoxy-6,7-methylenedioxyisoflavone): footnote 7*b*.
[19] Melting points are uncorrected. Ultra-violet spectra were measured in 95% ethanol solution on a Unicam S.P. 500 spectrophotometer and infra-red spectra in chloroform solution on a Baird double-beam recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

*2′,5,6-Trihydroxyflavone* (IIb) *from 2′,5,6-trimethoxyflavone* (IIa)

A solution containing 83 mg of the trimethoxy-compound IIa, 1 cc acetic anhydride and 3 cc hydriodic acid (*d.* 1·7) was heated in an oil bath at 140° for 2 hr. The solution was cooled, treated with ice-water and the resulting precipitate (70 mg) was collected, washed with water and dried. Crystallization from acetone–chloroform gave 2′,5,6-trihydroxyflavone (48 mg) as yellow needles, m.p. 278–280° dec. (reported:[12] m.p. 274–278° dec.); $\lambda_{max}$ 278 and 338 m$\mu$ (log $\varepsilon$, 4·65 and 4·37, respectively). It gave a stable yellow-brown colour with aqueous sodium hydroxide (two vicinal hydroxyl groups present).[12b] (Found: C, 66·37; H, 3·71; $CH_3O$, 0·00; act. H, 1·08. Calc. for $C_{15}H_{10}O_5$: C, 66·67; H, 3·73; 3 act. H, 1·12%).

2′,5,6-*Triacetoxyflavone* (IIc)

This substance was obtained from 2′,5,6-trihydroxyflavone (IIb) through boiling with sodium acetate in acetic anhydride for 1 hr. It formed colourless needles from methanol, m.p. 140–142° (reported:[13] m.p. 144–146°). (Found: C, 63·46; H, 3·84. Calc. for $C_{21}H_{16}O_8$: C, 63·63; H, 4·07%).

*2′,5,6-Trimethoxyflavone* (IIa) *from 2′,5,6-trihydroxyflavone* (IIb)

The trihydroxy-compound IIb (50 mg) was boiled under reflux for 6 hr with 5 g methyl sulphate and 10 g potassium carbonate in 30 cc dry acetone. Crystallization of the product from acetone gave 26 mg of the trimethoxy-compound IIa, m.p. 123–124°, undepressed on admixture with the natural compound.

*5-Hydroxy-2′,6-dimethoxyflavone* (IId)

(a) *From 2′,5,6-trimethoxyflavone* (IIa). The trimethoxy-compound IIa (100 mg) was boiled with 70 cc 20% hydrochloric acid for 30 min. The mixture was cooled, water was added and the yellow precipitate (90 mg) was collected, washed with water and dried. Crystallization from methanol gave 76 mg (80%) 5-hydroxy-2′,6-dimethoxyflavone as yellow needles, m.p. 153–154°; infra-red bands at 6·06, 6·18 and 6·33 $\mu$, no hydroxyl band in the 2·7–3·1 $\mu$ region[11]; $\lambda_{max}$ 272 and 329 m$\mu$ (log $\varepsilon$, 4·37 and 4·11, respectively). It gave a dark green colour with ethanolic ferric chloride (5-hydroxyl group present).[12a] (Found: C, 68·15; H, 4·81; $CH_3O$, 20·89; act. H, 0·38. $C_{17}H_{14}O_5$ requires: C, 68·45; H, 4·73; 2 $CH_3O$, 20·78; 1 act. H, 0·34%).

(b) *From 2′,5,6-trihydroxyflavone* (IIb). Treatment of the trihydroxy-compound IIb in methanol solution with excess ethereal diazomethane at 5° for 16 hr yielded over 90% of the 2′,6-dimethyl ether IId, m.p. 153–154°. There was no depression in m.p. on admixture with a sample prepared by method (a) and the infra-red spectra were identical.

*Fusion of 2′,5,6-trihydroxyflavone* (IIb) *with potassium hydroxide*

The powdered trihydroxy-compound IIb (130 mg) was added to 1·3 g potassium hydroxide and 0·2 cc water at 130°. The temperature was gradually increased to 170° during the next 30 min. More potassium hydroxide (0·3 g) was then added, the temperature raised to 210° during 15 min and kept there for a further 15 min. The clear brown melt was allowed to cool and water and dil hydrochloric acid were added. The product was extracted with ether and the ether layer was washed successively with sodium bicarbonate and sodium hydroxide solution. The bicarbonate extract was acidified with hydrochloric acid, extracted with ether and this ether solution dried and evaporated. Sublimation of the residue at 100° (25 mm) and subsequent crystallization from ether–hexane gave 35 mg (53%) salicyclic acid, m.p. 159–160°, identified with an authentic sample (m.p. 159–160°) through non-depression of the m.p. on admixture and the identity of the infra-red spectra.

The sodium hydroxide extract on acidification and extraction with ether gave 34 mg (26%) of the unchanged trihydroxy-compound IIb, but no other phenol could be identified.

*Comparison of synthetic with natural 2′,5,6-trioxygenated flavones*

Synthetic 2′,5,6-trimethoxyflavone (IIa) showed m.p. 122–124°, 2′,5,6-trihydroxyflavone (IIb) showed m.p. 275–278° dec., and treatment of the latter with diazomethane gave 5-hydroxy-2′,6-dimethoxyflavone (IId), m.p. 153–154°. There were no m.p. depressions when each of these substances were mixed with the corresponding natural derivative and the infra-red spectra in each case were identical.

*Zapotinin* (IIIb) *by treatment of zapotin* (IIIa) *with hydrochloric acid*

Zapotin[3] (200 mg) was boiled under reflux with 50 cc 20% hydrochloric acid for 1 hr. The substance soon dissolved, but a yellow precipitate then separated. Water was added and the precipitate was collected, dried and crystallized from methanol. The resulting zapotinin (175 mg; 91%) showed m.p. 223–224° and was identified with an authentic sample (m.p. 224–225°)[3a] by mixture m.p. determination and infra-red comparison. It gave a dark green colour with ethanolic ferric chloride; there was no hydroxyl band in the 2·7–3·1 $\mu$ region of the infra-red (5-hydroxyl group present).[10a,11]

*Zapotin* (IIIa) *by methylation of zapotinin* (IIIb)

Zapotinin (100 mg) was heated under reflux for 6 hr with methyl sulphate (10 g) and potassium carbonate (20 g) in dry acetone (60 cc). Crystallization of the product from methanol gave zapotin as colourless prisms, m.p. 149–151°, identified with an authentic sample (m.p. 150–151°)[3] in the usual way.

*Demethylzapotin* (IIIc)

This substance was obtained by treatment of zapotin with hydriodic acid and acetic anhydride as described previously.[3a] It showed m.p. 320–325° dec.: $\lambda_{max}$ 228, 270, 343, 349 and 366 m$\mu$ (log $\varepsilon$, 4·34, 4·32, 3·66, 3·65 and 3·61, respectively). An ethanolic solution gave a yellow colour with magnesium and hydrochloric acid (no 3-hydroxyl group).[12c] Addition of *p*-benzoquinone to an ethanolic solution resulted in no appreciable change of colour (no 5,8-dihydroxyl group).[13] A solution in 10% sodium hydroxide underwent colour changes from yellow to red-orange to green-brown to grey-brown within 20 min (at least three adjacent hydroxyl groups present).[12b,14] An ethanolic solution formed a green flocculent precipitate when heated with sodium amalgam (5,6,7-trihydroxy group present).[10c,17]

*Acknowledgements*—We are indebted to Dr. F. A. Kincl, Syntex S.A., Mexico City, for supplying us with crude casimiroin and with zapotin. We would also like to thank Prof. T. S. Wheeler and Dr. E. M. Philbin, University College, Dublin, for samples of synthetic 2′,5,6-trimethoxyflavone and 2′,5,6-trihydroxyflavone.

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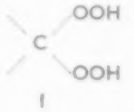
# ACCÈS À QUELQUES *gem*-MÉTHOXY HYDROPEROXYDES STÉROÏDES

L. VELLUZ, G. MULLER, J. MATHIEU et A. POITTEVIN
Centre de Recherches Roussel-Uclaf, Paris

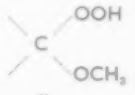
(*Received* 17 *December* 1959)

**Résumé**—L'ozonolyse en méthanol permet d'accéder, en série stéroïde, à des méthoxy-hydroperoxydes géminés. Des 20-cétopregnanes ont ainsi fourni des méthoxy-hydroperoxydes en 20, par l'intermédiaire d'un dérivé 20-méthylénique, ou en 17, par l'intermédiaire d'un acétate énolique.

NOUS avons précédemment décrit en série stéroïde plusieurs bis-hydroperoxydes géminés (I), obtenus par action du perhydrol sur les dérivés carbonylés correspondants.[1-4] Les éthers méthyliques correspondants, ou *gem*-méthoxy hydroperoxydes (II), déjà obtenus dans diverses séries,[5-7] ne semblent pas aisément accessibles à partir de la fonction cétonique. Nous avons donc opéré par ozonolyse d'une liaison éthylénique, en méthanol, suivant les résultats de Criegee.[8]

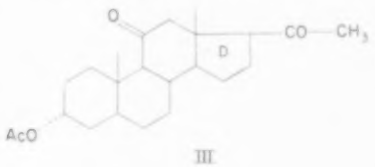



I

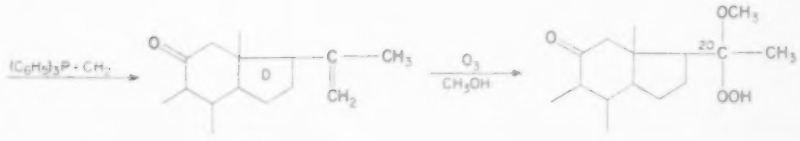



II

I(a) *Les 20-méthoxy 20-hydroperoxy stéroïdes* proviennent du clivage des dérivés 20-méthyléniques correspondants. L'accès à ceux-ci nous fut ouvert par la réaction de Wittig au méthylène-triphényl-phosphorane. Ainsi, le 3α-acétoxy 11,20-dicéto




III

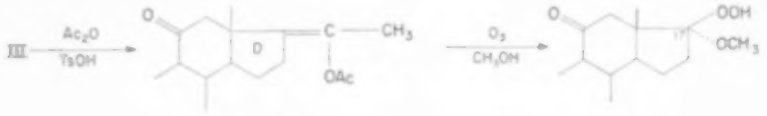



IV V

[1] J. Warnant, R. Joly, J. Mathieu et L. Velluz, *Bull. Soc. Chim. Fr.* 331 (1957).
[2] L. Velluz, G. Amiard, J. Martel et J. Warnant, *Bull. Soc. Chim. Fr.* 879 (1957).
[3] L. Velluz, G. Amiard, J. Martel et J. Warnant, *Bull. Soc. Chim. Fr.* 1484 (1957); *C. R. Acad. Sci., Paris*, **244**, 1937 (1957).
[4] L. Velluz, G. Amiard, J. Mathieu, J. Warnant, J. Martel et J. Valls, *Croatica Chem. Acta.* **29**, 255 (1957).
[5] R. Criegee et G. Lohaus, *Liebigs Ann.* **583**, 6 (1953).
[6] H. Plieninger et K. Suhr, *Chem. Ber.* **89**, 270 (1956).
[7] P. S. Bailey et S. S. Bath, *J. Amer. Chem. Soc.* **79**, 3120 (1957).
[8] R. Criegee et G. Wenner, *Liebigs Ann.* **564**, 9 (1949).

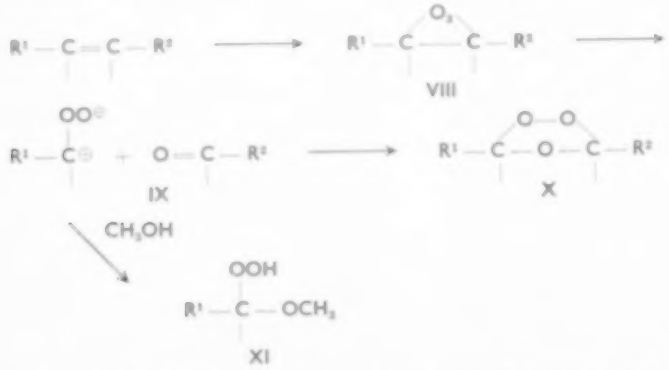
pregnane (III) fournit le composé 20-méthylénique (IV) ensuite soumis à l'action de l'ozone en méthanol, à −75°. Le rendement de l'ozonolyse atteint 70% en 3α-acétoxy 11-céto 20-méthoxy 20-hydroperoxy pregnane (V). Par réduction à l'aide du zinc en acide acétique, on régénère la cétone de départ.

1(b) *Les 17-méthoxy 17-hydroperoxy stéroïdes* n'exigent pas le passage par les dérivés 17-méthyléniques. Il est en effet plus commode de former les acétates énoliques des 20-céto pregnanes correspondants par l'anhydride acétique en présence d'acide fort. La pregnane 11,20-dione (III), précédemment citée, fournit dans ces conditions l'énol (VI) qui, après ozonolyse en méthanol, donne accès, avec un rendement de 85%, au 3α-acétoxy 11-céto 17-méthoxy 17-hydroperoxy étiocholane (VII). Le dérivé du pregnane exempt de carbonyle en 11 conduit de même au 3α-acétoxy 17-méthoxy 17-hydroperoxy étiocholane. La réduction par le zinc en acide acétique aboutit aux 17-céto étiocholanes correspondants.




VI VII

2—L'ozonolyse en méthanol procure d'intéressantes informations sur le mécanisme du clivage par l'ozone en général. Plusieurs hypothèses ont en effet été envisagées.[9] Selon Criegee,[5,10] l'ozonide (X) ne serait pas le produit primaire de la réaction. Il proviendrait de la recombinaison d'un zwitterion peroxydique (IX)—issu du clivage d'un complexe intermédiaire (VIII)—avec le fragment carbonylé. En présence de méthanol, ce zwitterion conduirait au méthoxy-hydroperoxyde (XI).

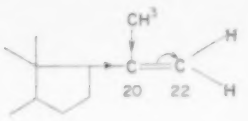



Alors que la symétrie de l'ozonide (X) ne permet pas de recconnaître le fragment de la molécule ayant conduit au zwitterion, la formation de méthoxy hydroperoxyde (XI) ne laisse aucun doute sur le sens du clivage du complexe intermédiaire (VIII).

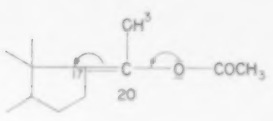
Les rendements satisfaisants en composés XI, que nous avons obtenus aussi bien à partir d'un dérivé méthylénique (XII) que d'un acétate énolique (XIII) n'étaient guère prévisibles. En effet, l'attaque électrophile de l'ozone doit porter sur les centres de

[9] P. S. Bailey, *Chem. Rev.* **58**, 926 (1956).
[10] R. Criegee, Abstracts of Papers presented at the 136th Meeting of the American Chemical Society, p. 87P (1959).

plus haute densité électronique. Or, l'effet électromère des alcoyles rend le centre 22 le plus sensible pour le dérivé XII et celui de l'acétoxyle sensibilise la position 17 du dérivé XIII.



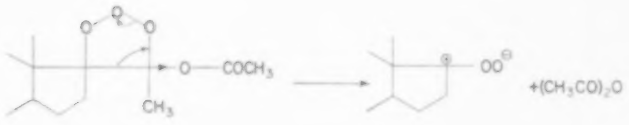

XII




XIII

Il apparaît donc bien que ce n'est pas l'attaque de l'ozone qui détermine la structure du produit final mais plutôt le sens du clivage de l'intermédiaire VIII. Ce clivage est dirigé par les effets inducteurs positif des alcoyles (XIV) et négatif de l'acétoxyle (XV).

XIV




XV

## PARTIE EXPERIMENTALE

*3α-Acétoxy 11-céto 20-méthylène pregnane* (IV). On chauffe au reflux pendant 1½ hr. 24 g de bromure de triphénylméthyl-phosphonium[11] dans 260 cm³ de benzène auxquels on a ajouté 48 cm³ de solution éthérée à 11% de phényl-lithium (1,3 M). On introduit ensuite 5 g de 3α-acétoxy 11,20-dicéto pregnane (III) (12) également dissous en benzène et poursuit le chauffage pendant 1½ hr. Après les traitements usuels, le produit brut de réaction est acétylé. On chromatographie sur alumine en éther de pétrole et sépare finalement 3,9 g (80%) de composé 20-méthylénique, F. 108–110°, $[\alpha]_D = +61°$ ($c = 0{,}5\%$, chloroforme). (Analyse: $C_{24}H_{36}O_3 = 372{,}5$. Calculé: C, 77,4; H, 9,7; O, 12,9; Trouvé: C, 77,2; H, 9,5; O, 12,9%).

*3α-Acétoxy 11-céto 20-méthoxy 20-hydroperoxy pregnane* (V). On dissout 0,5 g du composé méthylénique ci-dessus dans 5 cm³ de méthanol, refroidit à −75° et fait barboter un courant d'oxygène contenant 3% d'ozone à raison de 400 cm³/minute pendant ½ hr. Le produit cristallise peu à peu. Rendement: 0,38 g (68%), F. 170° (déc.). (Analyse: $C_{24}H_{38}O_6 = 422{,}5$. Calculé: C, 68,2; H, 9,1; O, 22,7; Trouvé: C, 68,9; H, 8,9; O, 23,1%).

*3α-Acétoxy 11-céto 17-méthoxy 17-hydroperoxy étiocholane* (VII). On dissout 1 g de 3α, 20-diacétoxy 11-céto $\Delta^{17(20)}$-pregnène (VI)[13] dans 50 cm³ de méthanol et ozonolyse comme ci-dessus, à température ordinaire. Rendement: 0,82 g (86%), F. 200–210° (déc.), $[\alpha]_D = +32°$ ($c = 0{,}5\%$, chloroforme). Analyse: $C_{25}H_{34}O_6 = 394{,}4$. Calculé: C, 67,0; H, 8,7; O, 24,3; Trouvé: C, 66,7; H, 8,6; O, 24,7%).

[11] G. Wittig et U. Schöllkopf, *Chem. Ber.* **87**, 1318 (1954).
[12] R. B. Turner, V. R. Mattox, W. F. McGuckin et E. C. Kendall, *J. Amer. Chem. Soc.* **74**, 5814 (1952).
[13] H. V. Anderson, E. R. Garrett, F. H. Lincoln, A. H. Nathan et J. A. Hogg, *J. Amer. Chem. Soc.* **76**, 743 (1954).

3α-*Acétoxy* 17-*méthoxy* 17-*hydroperoxy étiocholane*. On chauffe au reflux pendant 3 hr. 10 g de 3α-acétoxy 20-céto pregnane[14] dans 100 cm³ d'anhydride acétique contenant 0,75 g d'acide *p*-toluène sulfonique. On verse sur de la glace en présence d'acide sulfurique et extrait par le chlorure de méthylène. Le résidu, dissous dans 120 cm³ de méthanol, est soumis à l'ozonolyse comme ci-dessus. Rendement: 4,6 g (44%), F. 165° (déc.), $[\alpha]_D = +18°$ ($c = 0{,}5\%$, chloroforme). (Analyse: $C_{23}H_{36}O_5 = 380{,}5$. Calculé: C, 69,4; H, 9,5; O, 21,0; Trouvé: C, 69,4; H, 9,3; O, 21,2%).

[14] Ch. Meystre et K. Miescher, *Helv. Chim. Acta* **29**, 33 (1946).

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# REACTION OF POLYHALOMETHANES WITH ENOLETHERS OF $\Delta^4$-3-KETOSTEROIDS

## A NEW PATHWAY TO 6α-METHYLSTEROIDS

S. LIISBERG, W. O. GODTFREDSEN and S. VANGEDAL
Leo Pharmaceutical Products, Copenhagen

(*Received* 26 *January* 1960)

**Abstract**—Reaction of enol ethers of $\Delta^4$-3-ketosteroids with tetrabromomethane affords via 6-tribromomethylsteroids the corresponding 6-dibromomethylene-$\Delta^4$-3-ketosteroids. Upon catalytical hydrogenolysis over $Pd/SrCO_3$ these are smoothly transformed into 6-methyl-$\Delta^5$-3-ketosteroids, which without isolation are rearranged to 6α-methyl-$\Delta^4$-3-ketosteroids. Other polyhalomethanes react in a similar way with enol ethers of $\Delta^4$-3-ketosteroids.

INTRODUCTION of a 6α-methyl group in certain $\Delta^4$-3-ketosteroids causes a remarkable increase of their biological activities. Thus 6α-methylhydrocortisone and 6α-methylprednisolone, were found to be four times as active as hydrocortisone, and prednisolone respectively, in the glycogen deposition assay,[1] and 6α-methyl-17α-acetoxyprogesterone is one of the most active progestational agents yet known.[2]

The syntheses are generally [1–11]* based on the cleavage of a 3-hydroxy- or 3-cycloethylenedioxy-5α,6α-oxidosteroid with methylmagnesium halide to afford the 5α-hydroxy-6β-methyl system, from which the 6α-methyl-$\Delta^4$-3-ketone may be formed readily by conversion of the 3-hydroxyl group or 3-ketal to the 3-ketone, dehydration of the 5-hydroxyl group, and inversion of the 6β-methyl group.

Since the existing methods involve a Grignard reaction, it is necessary to protect other carbonyl functions in the molecule. Consequently, the total yields are often relatively low, and a simplified synthesis seemed therefore desirable.

In a search for new ways to introduce the 6-methyl group, the well known addition of polyhalomethanes to olefines[12] seemed to constitute an attractive possibility. This type of reaction, which has been extensively investigated by Kharasch, Haszeldine and others, is catalysed by light and peroxides, and is therefore considered to proceed by a free-radical mechanism. The reaction has, however, as far as we are aware, never been used in the steroid series.

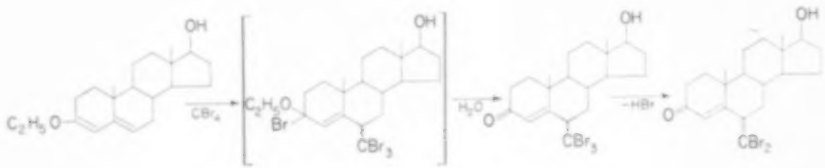
* See, however, references 6 and 8 where the authors describe alternative routes through a 6-keto-3,5-cyclosteroid or a 6-keto-5α-bromo-3β-acetate system.

[1] G. P. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[2] J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, *J. Amer. Chem. Soc.* **80**, 2904 (1958).
[3] H. J. Ringold, E. Batres and G. Rosencranz, *J. Org. Chem.* **22**, 99 (1957).
[4] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958).
[5] J. A. Campbell, J. C. Babcock and J. A. Hogg, *J. Amer. Chem. Soc.* **80**, 4717 (1958).
[6] D. Burn, B. Ellis, V. Petrow, J. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).
[7] M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and J. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).
[8] V. Greenville, D. K. Patel, V. Petrow, J. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4105 (1957).
[9] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).
[10] S. P. Barton, B. Ellis and V. Petrow, *J. Chem. Soc.* 478 (1959).
[11] O. S. Madaeva, M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem. U.S.S.R.* **10**, 213 (1940).
[12] Ch. Walling, *Free Radicals in Solution* pp. 247–272. John Wiley, New York (1957).

As starting material for such additions a steroid derivative containing a $\Delta^5$-double bond was necessary. Among easily obtainable derivatives of $\Delta^4$-3-ketosteroids fulfilling this requirement cyclic ketales, enol ethers, enol acetates, and enamines came into question. Of these, the enol ethers were soon found best suited, and only additions to this type of compounds will be dealt with in the following.

It will be shown that several polyhalomethanes, viz. $CBr_4$, $CCl_2Br_2$, and $CCl_3Br$ are able to react with enol ethers of $\Delta^4$-3-ketosteroids; of these $CBr_4$, however, has been found specially suited in the new synthesis of 6α-methyl steroids presented in this paper and reactions with this substance will therefore be treated in greater detail.

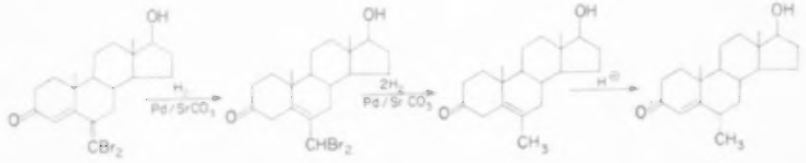
When a solution of testosterone 3-ethylenol ether (I) in collidine is treated with tetrabromomethane at room temperature, without any irradiation or addition of peroxides, a reaction takes place which, presumably through the intermediate II, leads to 6-tribromomethyltestosterone (III).




I II III IV

This compound readily eliminates hydrogen bromide with the formation of the crystalline, stable dibromomethylene compound IV.*

Upon catalytical hydrogenolysis over palladium on strontium carbonate in the presence of 2 moles of triethylamine, 3 moles of hydrogen are rapidly absorbed. The hydrogenolysis product contains no bromine and shows no selective absorption in the ultra-violet. In acid solution, however, it rearranges to a product, which in all respects is identical with authentic 6α-methyltestosterone (V), a result which is readily understood by assumption of the reaction sequence shown in formulae IV–V.




IV V

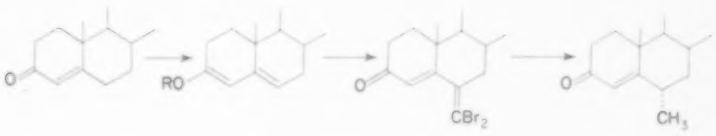
Besides testosterone the following $\Delta^4$-3-ketosteroids were transformed into their respective 6-dibromomethylene derivatives by reaction of their 3-ethylenol ethers with tetrabromomethane: 17α-methyltestosterone, 19-nor-testosterone, progesterone,

* The assignment of IV to the elimination product is based mainly upon infra-red evidence: Besides bands at 1660 and 1607 $cm^{-1}$ characteristic of the $\Delta^4$-3-keto system, the infra-red spectrum possesses a band at 1578 $cm^{-1}$, which could be due to the extra conjugated double bond present in IV. The possibility that one of the hydrogen atoms at $C_7$ has participated in the elimination with the formation of a cyclopropane ring can, however, not be excluded.

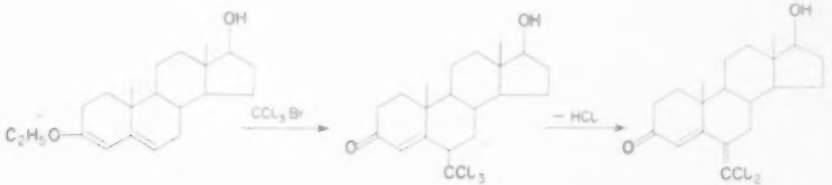
17α-hydroxyprogesterone, 11-desoxycorticosterone acetate, 17α-hydroxy-11-desoxycorticosterone acetate, and cortisone acetate. In most cases the tribromo-methyl compounds were not isolated, but directly transferred into the corresponding dibromomethylene compounds by heating the reaction mixtures. The yields varied from 30–80 per cent of the theoretical.

In contrast to 17α-hydroxyprogesterone, 6-dibromomethylene-17α-hydroxyprogesterone is acetylated at C-17 in nearly quantitative yield, a significant fact in the synthesis of the important progestational agent 6α-methyl-17α-hydroxyprogesterone.

All of the 6-dibromomethylene compounds, mentioned above, were readily converted into the corresponding 6α-methyl steroids by catalytical hydrogenolysis over $Pd/SrCO_3$ followed by an acid catalysed rearrangement. The hydrogenolyses were carried out in methyl cellosolve or dioxane in the presence of 2 moles of triethylamine, and the treatment with acid was performed directly on the hydrogenolysis mixtures after removal of the catalyst. The yields were mostly good, and the reaction sequence, shown below, therefore represents a convenient synthesis of 6α-methyl steroids.




It has already been mentioned that other polyhalomethanes react in a similar way as tetrabromomethane. Thus, treatment of testosterone 3-ethylenol ether (I) with $CCl_3Br$ in dioxane containing pyridine affords 6-trichloromethyltestosterone (VI), which readily eliminates hydrogen chloride to give 6-dichloromethylenetestosterone (VII),* a product which also is obtained if $CCl_3Br$ is replaced by $CCl_2Br_2$. In analogy with IV, VII upon catalytical hydrogenolysis followed by acid catalysed rearrangement smoothly affords 6α-methyltestosterone.




I VI VII

Since the completion of this work a new synthesis of 6α-methylsteroids, based upon hydroformylation of a starting material having a 5,6-double bond and no other reactive groups, is described.[13,14] The 6-formyl compounds formed during this reaction are reduced to the corresponding 6-hydroxymethyl compounds which via the tosylates are converted to 6α-methyl steroids.

* As regards the constitution of the elimination product the same considerations as stated for the corresponding dibromo compound are valid.

[13] A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman and J. Wender, *J. Amer. Chem. Soc.* **81**, 1228 (1959).

[14] P. F. Beal, M. A. Rebenstorf and J. E. Pike, *J. Amer. Chem. Soc.* **81**, 1231 (1959).

## EXPERIMENTAL

All melting points are corrected. Optical rotations, unless otherwise stated, were measured in chloroform and ultra-violet spectra in 96% ethanol solution. The infra-red spectra were obtained with a Perkin–Elmer Model 21 spectrophotometer with a sodium chloride prism.

*17α-Hydroxyprogesterone-3-ethylenol ether*

17α-Hydroxyprogesterone (66 g) and *p*-toluenesulphonic acid (200 mg) were dissolved in dry benzene (1000 ml). Ethyl orthoformate (33 ml) and abs ethanol (30 ml) were added, and the solution refluxed for 3 hr. After cooling and addition of pyridine (25 ml) the solution was washed with water (2 × 250 ml), dried, and evaporated *in vacuo*. The residue was recrystallized from methanol containing 0·5% pyridine to give *17α-hydroxyprogesterone-3-ethylenol ether* (49·5 g) m.p. 172–175°, raised by further crystallizations to 175–178°. (Found: C, 75·58; H, 9·59. $C_{23}H_{34}O_3$, $\frac{1}{2}CH_3OH$ requires: C, 75·36; H, 9·69%).

From the mother liquors 17α-hydroxyprogesterone (12·5 g) m.p. 218–219° was recovered by concentration and acidification with conc hydrochloric acid.

In the same manner the following enol ethers were synthesized:

*Testosterone-3-ethylenol ether:* m.p. 123–126°. Serini and Köster[15] report m.p. 118–122°.

*17α-Methyltestosterone-3-ethylenol ether:* m.p. 85–90°. (Found: C, 79·83; H, 10·15. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%).

*Progesterone-3-ethylenol ether:* m.p. 103–105°. (Found: C, 80·56; H, 10·04. $C_{23}H_{34}O_2$ requires: C, 80·65; H, 10·01%).

The 3-ethylenol ethers of *cortisone acetate* and *17α-hydroxy-11-desoxycorticosterone acetate* (*Reichsteins compound S acetate*) were prepared as described by Julian *et al.*[16] In a similar way the 3-ethylenol ether of *11-desoxycorticosterone acetate* was prepared. m.p. 138–140°. (Found: C, 74·52; H, 9·22. $C_{25}H_{36}O_4$ requires: C, 74·96; H, 9·06%).

*19-Nortestosterone-3-ethylenol ether*

To a solution of 3-ethoxy-19-nor-$\Delta^{3,5}$-androstadien-17-one[17] (10 g) in ether (500 ml) was added a solution of $LiAlH_4$ (3 g) in ether (200 ml). The mixture was refluxed for 1 hr and, after cooling, washed with saturated aqueous ammonium chloride and dried. After removal of the solvent the residue was crystallized from methanol to afford *19-nortestosterone-3-ethylenol ether* (9·9 g) m.p. 111–113°, raised by crystallization from methanol to 112–113°. (Found: C, 79·89; H, 9·94. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

*6-Tribromomethyltestosterone* (III)

*A.* Testosterone-3-ethylenol ether (31.6 g) was dissolved in freshly distilled 2,4,6-collidine (250 ml). Tetrabromomethane (66·4 g) was added, and, after standing for 48 hr at room temp, a precipitate consisting of collidine hydrobromide, $CBr_4$ was filtered off. With stirring, the filtrate was poured into chilled, dil hydrochloric acid, and the crystalline *tribromomethyltestosterone*, hereby precipitated, was collected on a filter, triturated with ether, followed by methanol and dried at room temp to give 45 g (83%) of material m.p. 215–216° (dec). U.V. $\lambda_{max}$ 238 mμ (ε 12900); I.R. ($CHCl_3$): 1600 and 1672 $cm^{-1}$. (Found: C, 44·60; H, 5·19; Br, 44·32. $C_{20}H_{27}Br_3O_2$ requires: C, 44·55; H, 5·05; Br, 44·47%).

*B.* Testosterone-3-ethylenol ether (3·16 g) was dissolved in propylene oxide (25 ml). Tetrabromomethane (3·32 g) was added, and the resulting solution exposed to direct sunlight. Shortly afterwards crystals began to separate. The reaction mixture was allowed to stand at room temp for 5 hr, whereafter the crystals were collected and washed with ether to yield 1·9 g *6-tribromomethyltestosterone* (m.p. 213–216°) identical with that prepared by method *A* above.

*6-Dibromomethylenetestosterone* (IV)

6-Tribromomethyltestosterone (5·39 g) in pyridine (100 ml) was heated on the steam bath for 30 min. After cooling, water was added, and the crystalline precipitate collected, and recrystallized

[15] A. Serini and H. Köster, *Ber. Dtsch. Chem. Ges.* **71,** 1766 (1938).
[16] P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *J. Amer. Chem. Soc.* **73,** 1982 (1951).
[17] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **76,** 4092 (1954).

from ethanol to give 4·05 g of material, m.p. 230–231°. The analytical sample, obtained by further recrystallizations from ethanol, had m.p. 232–233°. $[\alpha]_D^{20}$ +210°. U.V. $\lambda_{max}$ 250 mμ ($\varepsilon$ 10400), $\lambda_{shoulder}$ 285 mμ ($\varepsilon$ 6000); I.R. (KBr): 1578, 1607, 1660 cm$^{-1}$. (Found: C, 52·17; H, 5·72; Br, 34·88. $C_{20}H_{26}Br_2O_2$ requires: C, 52·42; H, 5·72; Br, 34·88%).

The acetate of IV was obtained directly from III as follows: To a solution of 6-tribromomethyltestosterone (5·7 g) in dry pyridine (65 ml) acetic anhydride (20 ml) was added. After standing overnight at room temp, the mixture was poured into water (500 ml). The precipitate was collected and recrystallized from ethanol to afford *6-dibromomethylenetestosterone acetate* (5·1 g), m.p. 168–169°. $[\alpha]_D^{20}$ +180°. I.R. ($CHCl_3$): 1570, 1610, 1675, 1725 cm$^{-1}$. (Found: C, 52·99; H, 5·78; Br, 31·98. $C_{22}H_{28}Br_2O_3$ requires: C, 52·81; H, 5·64; Br, 31·95%).

The following 6-dibromomethylene compounds were obtained in analogy with 6-dibromomethylenetestosterone, method *A* being used for the preparation of the intermediate 6-tribromomethyl steroids, which without purification, were converted to the corresponding dibromo compounds by heating in pyridine as described above.

6-*Dibromomethylene*-17α-*methyltestosterone*: m.p. 194–195° (from ethanol). $[\alpha]_D^{20}$ +193°; yield, 55%; U.V. $\lambda_{max}$ 251 mμ ($\varepsilon$ 10600), $\lambda_{shoulder}$ 285 mμ ($\varepsilon$ 5700). (Found: C, 53·48; H, 6·18; Br, 33·70. $C_{21}H_{28}Br_2O_2$ requires: C, 53·40; H, 5·97; Br, 33·85%).

6-*Dibromomethylene*-19-*nortestosterone acetate*: m.p. 146–147° (from methanol); yield, 35%; U.V. $\lambda_{max}$ 250 mμ ($\varepsilon$ 13900), $\lambda_{shoulder}$ 286 mμ ($\varepsilon$ 4900); I.R. (KBr): 1565, 1610, 1683, 1735 cm$^{-1}$. (Found: C, 51·93; H, 5·38; Br, 32·79. $C_{21}H_{26}Br_2O_3$ requires: C, 51·87; H, 5·39; Br, 32·87%).

6-*Dibromomethylene*-11-*desoxycorticosterone acetate:* m.p. 176–177° (from methanol). $[\alpha]_D^{20}$ +222°; yield, 45%; U.V. $\lambda_{max}$ 250 mμ ($\varepsilon$ 11400), $\lambda_{shoulder}$ 282 mμ ($\varepsilon$ 5000); I.R. (KBr): 1573, 1618, 1680, 1725, 1750 cm$^{-1}$. (Found: C, 52·91; H, 5·69; Br, 29·31. $C_{24}H_{30}Br_2O_4$ requires: C, 53·16; H, 5·57; Br, 29·47%).

The 6-dibromomethylene compounds of progesterone, 17α-hydroxyprogesterone, comp S acetate, and cortisone acetate were prepared by the following general procedure: The 3-ethylenol ether (0·1 mole) was dissolved in a mixture of dioxane (200 ml) and pyridine (16·1 ml ~ 0·2 mole). Tetrabromomethane (66·4 g ~ 0·2 mole) was added, and the resulting yellow solution was left standing at room temp for 24 hr. A crystalline precipitate, consisting of an addition compound of 1 mole pyridine hydrobromide and 1 mole tetrabromomethane was filtered off, and the filtrate heated on the steam bath for 3–4 hr. After cooling, a precipitate, mainly consisting of pyridine hydrobromide was removed; the filtrate was diluted with ether (500 ml), washed thoroughly with water, and dried; whereafter the solvent was removed *in vacuo*.

The residue crystallized with methanol, and the crude products, obtained in this way, were purified as follows:

6-*Dibromomethyleneprogesterone*. One recrystallization from methanol afforded 36% of material, m.p. 201–202°. The analytical sample had m.p. 202–203°. $[\alpha]_D^{23}$ +242°. U.V. $\lambda_{max}$ 250 mμ ($\varepsilon$ 9750), $\lambda_{shoulder}$ 285 mμ ($\varepsilon$ 5600); I.R. ($CHCl_3$): 1570, 1622, 1678 and 1700 cm$^{-1}$. (Found: C, 54·48; H, 5·82; Br, 32·95. $C_{22}H_{28}Br_2O_2$ requires: C, 54·58; H, 5·83; Br, 33·01%).

6-*Dibromomethylene*-17α-*hydroxyprogesterone*. After one recrystallization from methyl cellosolve 64% of prisms, m.p. 243–244° were obtained. The analytical sample had m.p. 246–247°. $[\alpha]_D^{22}$ +169°. U.V. $\lambda_{max}$ 252 mμ ($\varepsilon$ 10250), $\lambda_{shoulder}$ 280–285 mμ ($\varepsilon$ 5850). (Found: C, 52·93; H, 5·88; Br, 31·70. $C_{22}H_{28}Br_2O_3$ requires: C, 52·81; H, 5·62; Br, 31·95%).

6-*Dibromomethylene*-17α-*hydroxy*-11-*desoxycorticosterone acetate*. The crude product, which was contaminated with some comp S acetate, was dissolved in hot acetone. Upon cooling the impurity separated as needles. Addition of water to the filtrate precipitated the dibromo-compound, which was recrystallized from methanol to give a 30% yield of a product with m.p. 221–222°. The analytical sample, obtained from methyl cellosolve, had m.p. 228–229·5°. $[\alpha]_D^{20}$ +201°. U.V. $\lambda_{max}$ 251 mμ ($\varepsilon$ 9950), $\lambda_{shoulder}$ 280–285 mμ ($\varepsilon$ 5800). (Found: C, 51·61; H, 5·49; Br, 28·70. $C_{24}H_{30}Br_2O_5$ requires: C, 51·63; H, 5·42; Br, 28·63%).

6-*Dibromomethylenecortisone acetate*. A contamination of cortisone acetate was removed in the same way as the comp S acetate mentioned above. Recrystallization from methyl cellosolve afforded pure material with m.p. 236–237° in 55% yield. $[\alpha]_D^{20}$ +256°. U.V. $\lambda_{max}$ 252 mμ ($\varepsilon$ 9650), $\lambda_{shoulder}$ 275–280 mμ ($\varepsilon$ 5250); I.R. ($CHCl_3$): 1570, 1607, 1668, 1703, 1720 and 1735 cm$^{-1}$. (Found: C, 50·27; H, 5·12; Br, 27·96. $C_{24}H_{28}Br_2O_6$ requires: C, 50·37; H, 4·93; Br, 27·94%).

*Acetylation of 6-dibromomethylene-17α-hydroxyprogesterone*

6-Dibromomethylene-17α-hydroxyprogesterone (13·0 g) and *p*-toluene-sulphonic acid (13·0 g) were suspended in a mixture of glacial acetic acid (200 ml) and acetic anhydride (50 ml). The suspension was stirred until a clear solution resulted (about 1 hr) and then allowed to stand overnight at room temp. Water was added, and the amorphous precipitate collected on a filter, washed with water, and dried over $P_2O_5$. The dried product (14·2 g) was crystallized from benzene–hexane to give 14·6 g *6-dibromomethylene-17α-acetoxyprogesterone*, containing 1 mole of benzene: m.p. 111–115°.

For analytical purposes, a sample was recrystallized from benzene, m.p. 114·5–117°. $[\alpha]_D^{20}$ +143°. U.V. $\lambda_{max}$ 249 mμ (ε 10200), $\lambda_{shoulder}$ 280–285 mμ (ε 6200). (Found: C, 58·14; H, 6·06; Br, 25·72. $C_{24}H_{28}Br_2O_4$, $C_6H_6$ requires: C, 58·08; H, 5·85; Br, 25·76%).

TABLE 1

| Compound | M.p. | $[\alpha]_D$ | Recrystallized from | Yield[c] % | Ref. |
|---|---|---|---|---|---|
| 6α-Methyltestosterone[a] | 158–159° | +90° | acetone-hexane | 70 | 3, 5, 7 |
| 6α,17α-Dimethyltestosterone[a] | 137–139° | +66° | ether-hexane | 74 | 3, 5, 7, 8 |
| 6α-Methylnortestosterone acetate[a] | 126–128° | +8° | ether-hexane | 65 | |
| 6α-Methylprogesterone[a] | 122–123·5° | +177° | hexane | | 3, 6, 14 |
| 6α-Methyl-17α-acetoxyprogesterone[a] | 202–204° | +60·8° | isopropanol | 86 | 2, 10 |
| 6β-Methyl-17α-acetoxyprogesterone | 249–254° | +38·5° | methanol | | |
| 6α-Methyl-17α-hydroxy-11-desoxy-corticosterone acetate[a] | 198·5–200° | | acetone-hexane | 75 | |
| 6α-Methylcortisone acetate[a] | 240–241·5° | +219° | ethanol | 80 | 4 |

[a] The hydrogenation was performed in methyl cellosolve
[b] The hydrogenation was performed in dioxane
[c] The yields are based upon the amounts of material obtained after one recrystallization of the crude products

*6-Trichloromethyltestosterone* (VI)

To a solution of testosterone 3-ethylenol ether (20 g) in dioxane (60 ml), pyridine (5 ml) and bromotrichloromethane (10 ml) were added, and the mixture was allowed to stand at room temp for 20 hr. After filtration the filtrate was poured into a large amount of water, whereby an oil separated which, after decanting, was triturated with ether to give 12·5 g of crystals with m.p. 212–215° (dec). U.V. $\lambda_{max}$ 242 mμ (ε 12500). (Found: C, 59·87; H, 6·84; Cl, 26·90. $C_{20}H_{27}Cl_3O_2$ requires: C, 59·20; H, 6·71; Cl, 26·21%).

*6-Dichloromethylenetestosterone* (VII)

6-Trichloromethyltestosterone (VI, 10 g) was dissolved in pyridine (150 ml) and the solution heated on the steam bath for 30 min. After cooling, water was added, and on scratching the product crystallized. It was collected and recrystallized from ethanol to give 7·6 g of material, m.p. 208–210°. $[\alpha]_D^{20}$ +264°. U.V. $\lambda_{max}$ 246 mμ (ε 10400), $\lambda_{shoulder}$ 275 mμ (ε 5800); I.R. (KBr): 1612, 1665 $cm^{-1}$. (Found: C, 65·15; H, 7·20; Cl, 19·23. $C_{20}H_{25}Cl_2O_2$ requires: C, 65·04; H, 7·10; Cl, 19·20%).

*6α-Methyl-Δ⁴-3-ketosteroids*

*General procedure*. The 6-dibromomethylenesteroid (0·03 mole) was dissolved in methyl cellosolve or dioxane. Triethylamine (8·4 ml, 0·06 mole) was added, and the mixture shaken under hydrogen in the presence of 20 g of pre-reduced 2% palladium–strontium carbonate catalyst.[18]

[18] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* 74, 4223 (1952).

In 30–60 min, 3 moles of hydrogen were absorbed, and the consumption of hydrogen ceased. The catalyst was removed, and the filtrate acidified with 10% of 1 N hydrochloric acid. After standing for 1 hr at room temp water was added, and on scratching the product crystallized. It was filtered, washed with dil methanol, and, after drying, recrystallized from an appropriate solvent. The data of the hydrogenation products, which all gave satisfactory microanalyses, are given in Table 1.

By the hydrogenation of 6-dibromomethylene-17α-acetoxyprogesterone a small amount of 6β-methyl-17α-acetoxyprogesterone could be isolated from the mother liquor of the main product 6α-methyl-17α-acetoxyprogesterone. It was readily epimerized at C-6 upon treatment with hydrogen chloride in chloroform according to Campbell *et al.*[5]

*Acknowledgements*—The authors wish to thank Dr. P. Morch for I.R.- and U.V.-spectra and Mr. G. Cornali for the microanalyses.

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# STERIC HINDRANCE IN THERMAL AND CATALYSED ISOMERIZATIONS OF CHLORINATED α : α′-DICHLOROSTILBENES*

M. BALLESTER and J. ROSA
Departamento de Química Orgánica de Barcelona, Instituto de Química "Alonso Barba",
Consejo Superior de Investigaciones Científicas,
Universidad de Barcelona

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**Abstract**—Evidence is given for hindrance to thermal stereomutation of *cis*- and *trans*-perchlorostilbenes. Such hindrance is accounted for in terms of steric inhibition of resonance in the transition state of the isomerization due to the *ortho* chlorine atoms.

Also, it is shown that under conditions leading to isomerization in closely related cases, i.e. photochlorination and nuclear perchlorination, the perchlorostilbenes are quite inert. These results are interpreted in terms of steric strain of the reaction intermediates and transition states.

## *Thermal isomerization of stilbenes*

The thermal isomerization of stilbenes is easier than that of non-conjugated ethylenes such as 1,2-dideuteroethylene. This has been accounted for on the basis of single bond character of the ethylene bond in the ground state.[1] The effect is actually due to a lowering of the energy of activation† and therefore a more precise insight can be given when the energies, i.e. the resonance, of both ground and transition states of the molecule are taken into account.‡

It is generally assumed that the transition state in *cis–trans* thermal isomerizations is close to the so-called "perpendicular ethylene", i.e. the spatial molecular arrangement resulting after a 90° rotation around the ethylene bond axis of one ethylene carbon atom with the groups attached to it.[7] In such an arrangement, the ethylene carbon *p*-orbitals, which in the ground state form the π-bond, are perpendicular to each other and therefore the π-bond is practically broken.

In the case of stilbenes, resonance involving the *p*-orbitals of the ethylene carbon atoms and those of the benzene nuclei takes place. Any valence-bond structure participating in the ground state having a single bond between the ethylene carbon atoms participates to a much larger extent in the transition state of the isomerization

* Presented in *The XVI International Congress of Pure and Applied Chemistry*. Paris (1957). It contains part of the work done by J. Rosa in fulfilment of D.Sc.

† Reported values: 43 kcal/mol for *cis*-stilbene,[2] 61 kcal/mol for 1,2-dideuteroethylene,[3] and 52 kcal/mol for *cis*-2-butene.[4]

‡ It is generally accepted that the stilbenes isomerize by an "adiabatic" mechanism, i.e. a mechanism involving no singlet-triplet transitions.[5] The mechanism of the thermal isomerization of some strongly resonating substituted stilbenes is however uncertain.[6]

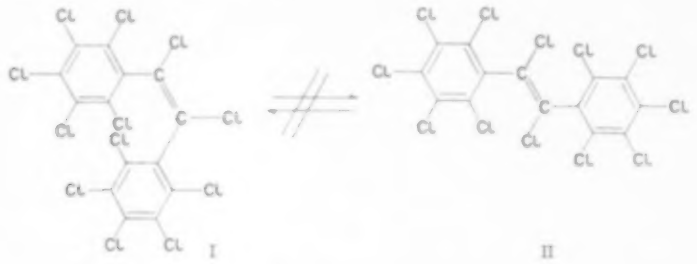
[1] G. W. Wheland, *Resonance in Organic Chemistry* p. 197. John Wiley, New York (1955).
[2] G. B. Kistiakowski and W. R. Smith, *J. Amer. Chem. Soc.* **56**, 638 (1934).
[3] B. S. Rabinovitch, J. E. Douglas and P. S. Looney, *J. Chem. Phys.* **20**, 1807 (1952).
[4] W. F. Anderson, J. A. Bell, J. M. Diamond and K. R. Wilson, *J. Amer. Chem. Soc.* **80**, 2384 (1958).
[5] J. L. Magee, W. Shand and H. Eyring, *J. Amer. Chem. Soc.* **63**, 677 (1941).
[6] M. Calvin and H. W. Alter, *J. Chem. Phys.* **19**, 768 (1951).
[7] L. Crombie, *Quart. Rev.* **6**, 101 (1952).

since the stability of this state is much more dependent on the contribution of such single-bond structures. In other words, stronger stabilization by resonance in the transition state than in the ground state must be the reason for the lower energy of activation in these isomerizations.

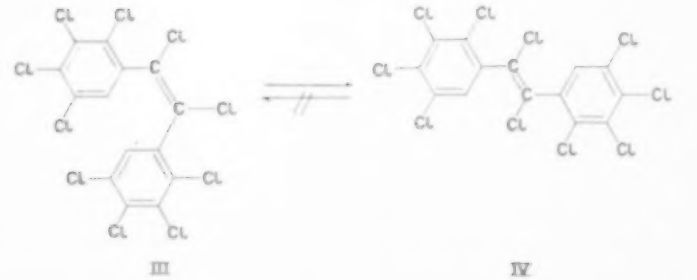
The conjugation between the ethylene bond and the benzene nuclei can be sterically inhibited in both ground and transition states by bulky substituents located in *alpha* and *ortho* positions. Their interactions prevent that degree of approach to coplanarity between the ethylene system and the benzene nuclei which is required to make the overlapping of *p*-orbitals effective.[8] The situation then approaches that of 1,2-dideuteroethylene, and the result should be a much more difficult thermal isomerization.

In Fig. 1 the transition state for the perchlorostilbenes is represented. The shaded areas show the steric interaction between chlorine atoms causing the departure from coplanarity in the transition state. Accordingly, while *cis*-α,α′-dichlorostilbene undergoes measurable isomerization in the liquid phase at around 200°[9] here it is reported that extended heating of *cis*-perchlorostilbene (I) at 300°, or *trans*-perchlorostilbene (II) at 400°, fails to give any detectable isomerization.

It can be expected that removal of one *ortho* chlorine in both benzene nuclei of perchlorostilbene would strongly diminish the inhibition of resonance in the transition state. Actually, 1·5 hr heating of *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene (III) at 260° yields an 11 per cent conversion into its *trans*-isomer (IV). This isomer fails to give any *cis*-isomer under the same conditions.



I II



III IV

*Catalytic isomerizations of stilbenes*

Halogen atoms can bring about *cis–trans* isomerizations. The evidence reported in the literature points to a radical chain mechanism occuring essentially in three

[8] M. Ballester, C. Molinet and J. Rosa, *Tetrahedron* **6**, 109 (1959).
[9] T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.* 2078 (1938).

steps:[10] (1) Reversible halogen-atom addition to double bond. (2) Rotation isomerization of the resulting radical-adduct to give that of the isomeric ethylene. (3) Reversible dissociation of this second adduct to yield the isomeric ethylene.

The main feature of this mechanism is that with the addition process the high rotational energy barrier of an ethylene bond is replaced by the smaller rotational energy barriers of a single bond between a tetrahedral and a trigonal carbon atom.

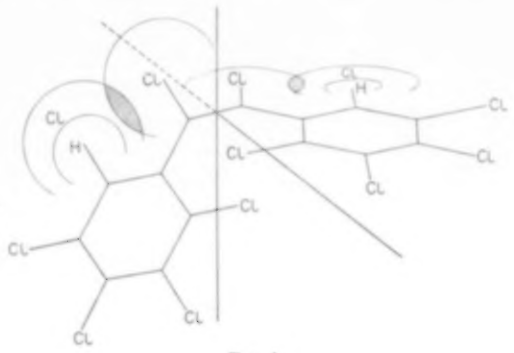



FIG. 1.

If this isomerization mechanism is accepted it can be expected that the introduction in a stilbene of bulky groups in *ortho* and *alpha* positions should prevent its isomerization by halogen either hindering step (1) or (2). This should be the case of perchlorostilbene. Its hypothetical radical adducts with a chlorine atom, IA and IIA, should possess an important steric strain due to overcrowding about the carbon (tetrahedral) atom to which the chlorine atom becomes bonded. This strain would assist the dissociation of the adducts into their original components.

There is a considerable body of evidence showing that compounds of the type $C_6Cl_5CCl_2R$ ($R = Cl$, $CCl_3$, $CCl_2C_6Cl_5$, etc.), because of the steric repulsions between the two *ortho* chlorine atoms and the substituents on the *alpha* carbon atom, are energy-rich. In spite of the great number of attempted preparations few of such compounds have been obtained so far.[11] Their ultra-violet absorption spectra reflect strikingly their high strain.[12] Brown *et al.* have estimated on experimental basis the strain of 2,6-dichloro-1-trichloromethylbenzene;[13] their value is 24 kcal/mol. This means that in the case of the perchlorostilbenes there is an additional steric energy barrier to be surmounted in step (1) which obviously is high enough to break up the reaction chain.

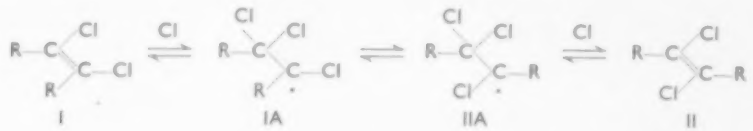
It is pointed out that step (1) is an electrophylic attack and therefore it is favoured by electron release to the *alpha* carbon atom. Therefore, it can be expected that steric inhibition of resonance between the benzene nuclei and the double bond due to steric interaction between the two *ortho* chlorine atoms and the substituents attached to the *alpha* carbon atom can hinder that electron accession to the reaction site and consequently also step (1).* However, in view of the magnitude of the energy due to

* The authors are much indebted to the referee of this work for pointing out such possibility and for other valuable suggestions.

[10] H. Steinmetz and R. M. Noyes, *J. Amer. Chem. Soc.* **74**, 4141 (1952).
[11] M. Ballester, C. Molinet and J. Castañer, forthcoming publication.
[12] M. Ballester and J. Castañer, forthcoming publication.
[13] H. C. Brown, D. Gintis and L. Domash, *J. Amer. Chem. Soc.* **78**, 5387 (1956).

overcrowding and the very small extent of the "styrene" resonance in *both* α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbenes and perchlorostilbenes as ascertained by their ultraviolet spectra[8] and by simple inspection of their Stuart models, the authors do not favour this effect as a major one.

The radical adducts should also have to overcome an important steric energy barrier before reaching the required configuration for step (3) of the isomerization to occur. This would create an additional hindrance and favour further the ineffectual dissociation of the adducts over the stereomutation.




It has been found accordingly that while an attempted photochlorination with chlorine and white light of *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene gives 84·6 per cent yield of its isomer, both *cis*- and *trans*-perchlorostilbene fail to give any detectable isomerization under the same conditions. No isomerization of the *cis*-decachlorostilbene occurs by illumination with white light in the absence of chlorine, the other conditions being equal.

*trans*-α,2,3,4,5,α′,2′,3′,4′,5′-Decachlorostilbene gives, when treated with sulphuryl chloride containing anhydrous aluminium chloride and sulphur monochloride, an almost quantitative yield of *trans*-perchlorostilbene. However, when *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene is treated with the same reagent and under the same conditions a mixture containing both the *cis*- and *trans*-perchlorostilbene is obtained. Therefore, by the influence of the chlorinating agent stereomutation has occurred.

It has been found that neither *cis*- nor *trans*-perchlorostilbene isomerizes under the reaction conditions. Therefore, the stereomutation has taken place either in the decachlorostilbene or in the undecachlorostilbene stage.

If it is accepted—as in the previously considered case of the radical-catalysed isomerization—that the isomerization here occurs through double-bond addition of an electrophylic particle, it is reasonable to assume that the stereomutation will take place the easier the lesser is the degree of *ortho* substitution by chlorine. In the present case, the hindrance to isomerization in the perchlorostilbenes is interpreted also through consideration of the high steric strain of the intermediate adducts. It can therefore be assumed that stereomutation occurs, at least mostly, prior to any nuclear perchlorination.

The fact that isomerization occurs in a relatively chlorine overcrowded compound such as *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene suggests that the electrophylic particle which adds to the double bond is a small one. One is tempted to assume that $Cl^+$ is the particle and, consequently, that the isomerization occurs through the intermediate cation $C_6HCl_4CCl_2—\overset{+}{C}Cl—C_6HCl_4$.

## EXPERIMENTAL

Some properties of the stilbenes here studied have been given previously.[8] However, it is desirable to emphasize here again that the great differences of solubility between the geometrical isomers permitted treatment with solvent to perform clean and relatively rapid separations.

Some experiments described are intended to show that the isomerization of perchlorostilbenes, if any, is insignificant. It was desirable therefore to perform control experiments concerning the solubilities in the solvents used under the separation conditions to find out whether considerable amounts of the isomers could pass undetected.

*Solubility experiments*

Finely ground perchlorostilbene was shaken in the solvent during 1½ hr at 16–17°. The undissolved part was filtered off and the residue of a measured part of the solution was weighed.

*Ethyl ether cis*-perchlorostilbene, 0·41 g% ml; *trans*-perchlorostilbene, 0·0040%. *Benzene cis*-perchlorostilbene, 5·70%; *trans*-perchlorostilbene, 0·015%.

The solubilities of *trans*-perchlorostilbene in saturated solution of *cis*-perchlorostilbene are: *Ethyl ether* 0·0044%. *Benzene* 0·016%.

Consequently, the differences of solubility and the insolubility of the *trans* isomer are so great as to permit exceptionally clean separations.

*Thermal isomerization of* cis-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene*

In a sealed glass tube 0·106 g *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene, m.p. 141–142°,[9] were heated during 6 hr at 260–265°. The resulting solid mass was treated with boiling pet ether which extracted 0·092 g of the starting material. The residue (0·012 g) was identified as *trans*-decachlorostilbene by m.p., mixed m.p. and ultra-violet spectrum.[8] The yield of the isomerization was therefore 11·3%.

*Attempted thermal isomerization of* trans-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene*

In a sealed glass tube 0·079 g *trans*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene, m.p. 255–257°,[8] were heated during 1·5 hr at 265°. The resulting mass was refluxed with 10 ml pet ether and the residue (0·068 g) was identified by m.p. and mixed m.p. as unchanged *trans*-decachlorostilbene. Concentration of the mother liquor yielded 0·007 g more starting material. No *cis*-decachlorostilbene was detected.

*Attempted thermal isomerization of* cis-*perchlorostilbene*

In a sealed glass tube 0·211 g *cis*-perchlorostilbene, m.p. 230·5–231·5°,[9] were heated during 4 hr at 300°. The resulting mass (0·210 g) left no insoluble residue by treatment with a few ml cold benzene, and it was identified as starting material by m.p. and mixed m.p.

*Attempted thermal isomerization of* trans-*perchlorostilbene*

In a sealed glass tube 0·078 g *trans*-perchlorostilbene, m.p. 390°,[9] were heated during ½ hr at 400°. Treatment of the resulting mass with hot carbon tetrachloride gave 0·018 g pure starting material as residue. The carbon tetrachloride solution, after evaporation to dryness and treatment with hot benzene gave 0·053 g more starting material. The part soluble in benzene (0·006 g) gave by concentration 0·003 g more *trans*-perchlorostilbene and 0·003 g of an oil which did not yield crystals, even when seeded with *cis*-perchlorostilbene. The recovered material melted sharply at 390° and it was identified by mixed m.p.

*Attempted photochlorination of* cis-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene*

Through a steam-heated solution of 0·052 g *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene in 3 ml purified carbon tetrachloride placed in a "Pyrex"-brand container a stream of dry chlorine was passed while illuminating with a 500W incandescent lamp located at 20 cm from the container. Partial removal of the solvent yielded 0·023 g *trans*-decachlorostilbene which was identified by m.p., mixed m.p. and ultra-violet spectrum.[8] The residue obtained by total elimination of the solvent was treated with hot pet ether yielding 0·021 g more of the product. Yield of the isomerization, 85%.

*Attempted photo-isomerization of* cis-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene with white light*

A solution of 0·050 g *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene in 3 ml purified carbon tetrachloride was heated during 22 hr in a "Pyrex"-brand flask while illuminating with a 500W incandescent lamp located at 20 cm from the container. Removal of the solvent gave 0·049 g unchanged pure *cis*-decachlorostilbene. It was identified by mixed m.p.

*Attempted photochlorination of* cis-*perchlorostilbene*

Through a steam-bath heated solution of 0·200 g *cis*-perchlorostilbene in 7·5 ml purified carbon tetrachloride a stream of dry chlorine was passed during 19·5 hr while illuminating with a 500W incandescent lamp situated at 20 cm from the container. By removal of the solvent 0·239 g of a solid residue was obtained which by digestion in ethanol gave 0·189 g starting material. From the ethanol solution 0·05 g perchloroethane was obtained. The recovered *cis*-perchlorostilbene melted at the correct temperature and was completely soluble in cold ethyl ether. This showed the absence of a significant amount of the *trans*-isomer.

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*Attempted photochlorination of* trans-*perchlorostilbene*

Through a steam-bath heated suspension of 0·200 g *trans*-perchlorostilbene in 7·5 ml purified carbon tetrachloride a stream of dry chlorine was passed during 35 hr while illuminating with a 500W incandescent lamp situated at 20 cm from the container. The solid residue obtained by elimination of the solvent was treated with hot pet ether leaving 0·174 g of a residue which was identified as starting material. The soluble part consisted of perchlorobenzene (0·020 g) and perchloroethane the separation of which was performed by treatment with ethanol. The identification was performed by mixed m.p. with authentic samples. The *trans*-perchlorostilbene melted sharply at 390°.

*Nuclear chlorination of* cis-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene*

A solution containing 0·050 g sulphur monochloride in 4 ml of sulphuryl chloride was added gradually to a boiling solution containing 0·100 g *cis*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene, 0·025 g anhydrous aluminium chloride and 3 ml sulphuryl chloride. The resulting solution was then concentrated to 2 ml and the refluxing continued for about 3 hr, keeping constant the volume of the reaction mixture by adding small quantities of sulphuryl chloride. Most of the sulphuryl chloride was distilled off and the residue treated with hot water and powdered sodium bicarbonate. The mass was then acidified with hydrochloric acid to dissolve the aluminium hydroxide formed, treated with ethyl ether and the two layers formed filtered. The insoluble part (0·038 g) was identified as *trans*-perchlorostilbene by m.p., mixed m.p. and ultra-violet spectrum.[8]

By removing the ether from the ethereal layer a solid was obtained which by recrystallization from ethyl acetate gave 0·047 g *cis*-perchlorostilbene, being identified by m.p., mixed m.p. and ultra-violet spectrum.[8] The yields were 33·6% *trans*-isomer and 41·5% *cis*-isomer.

*Nuclear chlorination of* trans-α,2,3,4,5,α′,2′,3′,4′,5′-*decachlorostilbene*

A solution of 0·100 g sulphur monochloride in 8 ml sulphuryl chloride was added gradually to a refluxing solution containing 0·100 g *trans*-α,2,3,4,5,α′,2′,3′,4′,5′-decachlorostilbene, 0·050 g anhydrous aluminium chloride and 6 ml sulphuryl chloride. The mass was then concentrated to 10 ml and the refluxing continued for about 3 hr as above. The part insoluble in ether (0·118 g) was treated with warm carbon tetrachloride and gave a residue (0·089 g) identified as *trans*-perchlorostilbene by m.p. (390°, sharply), mixed m.p. and ultra-violet spectrum. The part soluble in carbon tetrachloride was washed with pet ether and left 0·023 g more pure *trans*-perchlorostilbene. Yield: 99·1% of the theoretical.

*Attempted isomerization of* cis-*perchlorostilbene under the nuclear chlorination conditions*

0·300 g *cis*-perchlorostilbene were treated with a mixture containing 0·075 g anhydrous aluminium chloride, 0·150 g sulphur monochloride and 21 ml sulphuryl chloride under the usual conditions, reducing the volume to 2 ml and refluxing during 3 hr. The resulting mass was treated with water solid sodium bicarbonate and acidified with conc hydrochloric acid. The solid residue was filtered off and dried (0·285 g). It melted at 230·0–231·5° and it was identified as pure starting material by mixed m.p. and ultra-violet spectrum. It was soluble in cold ethyl ether leaving no residue.

Trans-*perchlorostilbene under nuclear chlorination conditions*

A solution of 0·050 g sulphur monochloride in 4 ml sulphuryl chloride was added gradually to a gently boiling solution of 0·116 g *trans*-perchlorostilbene, 0·025 g anhydrous aluminium chloride and 3 ml sulphuryl chloride. It was then concentrated to 1–2 ml and the refluxing continued for 2 hr 40 min more. The resulting mass was treated as usual and gave a solid residue (0·114 g) which

was treated during ½ hr with boiling ether. The insoluble part (0·105 g) was identified by m.p. and mixed m.p. as starting material. From the ethereal extract by elimination of the solvent a residue (0·009 g) was obtained. This was dissolved in carbon tetrachloride and passed through a very small amount of activated alumina, and the resulting solution evaporated to dryness. The residue was treated with a very small amount of hot pet ether leaving after standing 0·005 g more *trans*-perchlorostilbene melting sharply at 390°. The remaining 0·002 g was a mixture melting poorly containing presumably some *trans*-perchlorostilbene. The ultra-violet spectra confirmed his assumption, giving no indication of the *cis*-isomer being present.

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# ELECTRONIC ABSORPTION SPECTRA OF ALKYL- AND PHENYL-SUBSTITUTED PYRYLIUM SALTS

A. T. BALABAN, V. E. SAHINI and (Miss) E. KEPLINGER
Laboratory of Organic Chemistry, Politechnical Institute; Institute of Atomic Physics; Laboratory of Physical Chemistry, C. I. Parhon University; Bucharest

(*Received* 2 *November* 1959)

**Abstract**—Absorption spectra in the region 220–400 mμ have been determined for alkyl- and phenyl-substituted pyrylium salts. Three bands are apparent, in the decreasing order of wavelength, *x*, *y*, and *x'* bands. These bands are differently influenced by substitution in α and γ positions. Relationships of these bands with transitions in other aromatic compounds are established, and the effect of heteroatom variation in the series III–VI on the spectrum is discussed.

FROM the following series of six-membered monocyclic monoheteroaromatic systems, compounds II–VI are known (as well as the thiapyrylium cation VII, related to VI). The pyrylium cation VI contains a heteroatom $O^{\oplus}$ with the greatest electronegativity in the series I–VI[1] and therefore, although it is much more stable than an ordinary oxonium cation (because of the aromatic conjugation), it is much more reactive than the other aromatic systems and it can easily be converted into them.[2]

VI → III, IV, V or VII

I II III IV V VI VII

The electronic absorption spectra of the pyrylium cation or its derivatives with simple alkyl or phenyl substituents have been determined only in two isolated cases. The ultra-violet absorption spectrum of 2,4,6-trimethylpyrylium perchlorate* in ethanol solution has been determined in connection with the problem of pyrone mesomerism.[3] More systematically, the visible and ultra-violet absorption spectra of substituted pyrylium salts have been determined by Wizinger *et al.*;[4–8] they have described the spectrum of 2,4,6-triphenylpyrylium perchlorate in acetic acid[4–7] and of many other pyrylium salts with auxochromes, in a comprehensive study of the

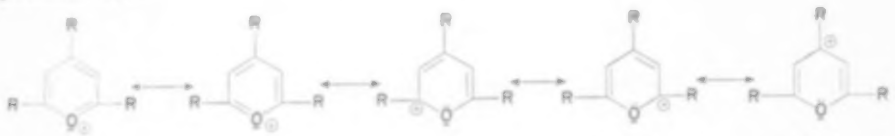
* It had been qualitatively reported in $H_2SO_4$ by A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **52**, 1535 (1919).

[1] A. T. Balaban, *Studii Cerc. Chim.* **7**, 257 (1959).
[2] A. T. Balaban and C. D. Nenitzescu, *Liebigs Ann.* **625**, 74 (1959).
[3] R. C. Gibbs, J. R. Johnson and E. C. Hughes, *J. Amer. Chem. Soc.* **52**, 4895 (1930).
[4] R. Wizinger and K. Wagner, *Helv. Chim. Acta* **34**, 2290 (1951).
[5] R. Wizinger, A. Grüne and E. Jacobi, *Helv. Chim. Acta* **39**, 1 (1956).
[6] R. Wizinger, S. Losinger and P. Ulrich, *Helv. Chim. Acta* **39**, 5 (1956).
[7] R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 207 (1956).
[8] R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 217 (1956).

influence of auxochromes on the spectra of cations V, VI and VII and the respective cyanines (but limiting themselves to the band with longer wavelength and not giving extinction coefficients).

The electronic absorption spectra of simple substituted, auxochrome-free pyrylium salts (which should reflect the electronic correlations in the series I–VI) have not yet been systematically investigated. Such studies exist in the benzopyrylium series[9] and in other polycyclic pyrylium compounds. The scope of the present paper is to fill this gap, and to furnish the basis for a comparative discussion of the systems I–VI. All but one pyrylium salt studied in the present paper have been obtained by a new simple synthetic method.[2]

The unsubstituted pyrylium cation is very unstable;[10] it may be isolated only at low temperature but it decomposes quickly. This may be explained by the mesomerism depicted in the formulae VIII. The large electronegativity of the oxygen heteroatom causes the positive charge to appear in positions 2 and 6($\alpha$) and somewhat less in position 4($\gamma$).



VIII a VIII b VIII c VIII d VIII e

In the case of unsubstituted pyrylium salts (VIII, R = H), the 2,4 and 6 carbon atoms behave as secondary carbonium ions which are highly reactive and unstable. But the systems bearing substituents in these positions (VIII, R = Alk or Ar) are stable, because tertiary carbonium ions are stable (even the simplest tertiary carbonium ion, $(H_3C)_3C^{\oplus}$ has been spectroscopically identified in dilute solution).[11] These substituted systems constitute the object of the present study.

The perchlorate anion has been chosen for all pyrylium salts because it is synthetically and spectroscopically convenient, and gives stable and easily purified salts. Owing to the very small basicity of the $ClO_4^{\ominus}$ anion, no electronic interactions[12] are to be expected.

TABLE 1. EFFECT OF THE SOLVENT ON THE ABSORPTION SPECTRUM OF 2,4,6-TRIMETHYLPYRYLIUM PERCHLORATE (IX, $R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $X = ClO_4$)

| No. | Solvent | Conc. moles/l | *y* Band | | *x* Band | |
|---|---|---|---|---|---|---|
| | | | $\lambda_{max}$ (m$\mu$) | $\varepsilon_{max}$ | $\lambda_{max}$ (m$\mu$) | $\varepsilon_{max}$ |
| 1.1 | water | $10^{-5}$ | 233 | 5450 | 284 | 7900 |
| 1.2 | ethanol* | $10^{-5}$ | 232 | 4500 | 286 | 9260 |
| 1.3 | acetic acid | $10^{-3}$ | — | — | 284 | 12020 |
| 1.4 | 0·05 N $HClO_4$ | $10^{-3}$ | 230 | 4550 | 285 | 12000 |

* Literature values[9] $\lambda_{max}$ 230 m$\mu$, $\varepsilon_{max}$ 3650 and $\lambda_{max}$ 286 m$\mu$, $\varepsilon_{max}$ 10400

[9] A. N. Nesmeyanov, L. A. Kazytsina, N. K. Kochetkov and M. I. Rybinskaya, *Izv. Akad. Nauk, OHN* 784 (1954).

[10] F. Klages and H. Träger, *Chem. Ber.* **86**, 1327 (1953).

[11] J. Rosenbaum and M. C. R. Symons, *Proc. Chem. Soc.* 92 (1959).

[12] F. Kröhnke and H. Dickoré, *Chem. Ber.* **92**, 46 (1959) and especially p. 53.

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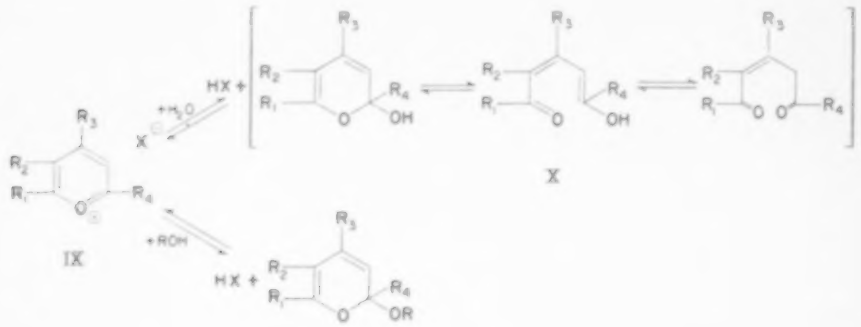
1. *The effect of the solvent* has been studied for 2,4,6-trimethylpyrylium perchlorate (Table 1). The absorption maxima in water, ethanol, acetic acid and aqueous 0·05 N perchloric acid appear at nearly equal wavelengths, but in the first two cases (1.1 and 1.2) the extinction coefficients are smaller, and prolonged irradiation or conservation is reducing and shifting these maxima.

This may be explained by admitting partial solvolysis leading to tautomeric pseudobases X[13] or to ethers XI:




X XI

In acid solution, the formation of such compounds X or XI which polymerize or decompose on irradiation or conservation, is prevented by shifting the equilibrium towards the pyrylium cation IX.

The work was therefore continued only with solutions in aqueous 0·05 N perchloric acid (for pyrylium salts containing 0 or one phenyl group) or in acetic acid (for pyrylium salts containing two or more phenyl groups, which are sparingly soluble in water). These solutions are stable to irradiation giving reproducible results. The lower limit of the spectrum is 220 m$\mu$ for solutions in aqueous perchloric acid and 235 m$\mu$ for solutions in acetic acid.

2. *The spectra of pyrylium salts with alkyl groups in* 2,4 *and* 6 *positions* contain two bands with maxima at 230–235 m$\mu$ (designated *y band*) and at 285–290 m$\mu$ (*x band*); the effect of the alkyl groups is rather small, as shown in Table 2.

Though the variations are small, they are greater than experimental errors, so that some general conclusions may be reached.

In Fig. 1, $\lambda_{max}$ and $\varepsilon_{max}$ of alkyl-substituted pyrylium perchlorates have been related to the number of carbon atoms in their formulae (Table 2). Each point in Fig. 1 is numbered in accordance with Table 2. The effects of substitutents upon wavelength and absorption intensity have been separately represented for the *x* and *y* bands. The following general trends may be observed.

(*a*) The increase of the alkyl group in α-position in the order Me → Et → iPr → tBu corresponding to the increase of the number of carbon atoms, of the volume, and of the electron-repelling inductive effect (2.1, 2.3, 2.5, 2.6 and 2.7), has a small effect on the *y* band ($\lambda_{max}$ and $\varepsilon_{max}$ have a very slight increase), but has a sensible influence on the *x* band ($\lambda_{max}$ increases little and $\varepsilon_{max}$ increases appreciably). These variations are indicated by the full lines in Fig. 1.

[13] J. A. Berson, *J. Amer. Chem Soc.* **74**, 358 (1952).

Table 2. Absorption spectra of alkyl-substituted pyrylium perchlorates
(IX, X = $ClO_4$; $10^{-3}$ molar solutions in 0·05 N perchloric acid)

| No. | Substituents in IX | | | | Formula | *y* Band | | | | *x* Band | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | | $\lambda_{max}$ (mμ) | $\nu_{max}$ ($cm^{-1}$) | $\varepsilon_{max}$ | lg $\varepsilon_{max}$ | $\lambda_{max}$ (mμ) | $\nu_{max}$ ($cm^{-1}$) | $\varepsilon_{max}$ | lg $\varepsilon_{max}$ |
| 2.1 | $CH_3$ | H | $CH_3$ | $CH_3$ | $C_8H_{11}O^{\oplus}$ $ClO_4^{\ominus}$ | 230 | 43480 | 4550 | 3·658 | 285 | 35090 | 12000 | 4·079 |
| 2.2 | $CH_3$ | H | $C_2H_5$ | $CH_3$ | $C_9H_{13}O^{\oplus}$ $ClO_4^{\ominus}$ | 233 | 42920 | 5950 | 3·775 | 285 | 35090 | 12200 | 4·086 |
| 2.3 | $CH_3$ | H | $CH_3$ | $C_2H_5$ | $C_9H_{13}O^{\oplus}$ $ClO_4^{\ominus}$ | 231 | 43290 | 4610 | 3·664 | 286 | 34960 | 12900 | 4·111 |
| 2.4 | $CH_3$ | H | $CH(CH_3)_2$ | $CH_3$ | $C_{10}H_{15}O^{\oplus}$ $ClO_4^{\ominus}$ | 236 | 42370 | 6120 | 3·787 | 285 | 35090 | 11560 | 4·063 |
| 2.5 | $C_2H_5$ | H | $CH_3$ | $C_2H_5$ | $C_{10}H_{15}O^{\oplus}$ $ClO_4^{\ominus}$ | 231 | 43290 | 4650 | 3·667 | 287 | 34840 | 13250 | 4·122 |
| 2.6 | $(H_3C)_2CH$ | H | $CH_3$ | $CH(CH_3)_2$ | $C_{12}H_{19}O^{\oplus}$ $ClO_4^{\ominus}$ | 232 | 43100 | 4680 | 3·670 | 288 | 34720 | 13860 | 4·142 |
| 2.7 | $(H_3C)_3C$ | H | $CH_3$ | $C(CH_3)_3$ | $C_{14}H_{23}O^{\oplus}$ $ClO_4^{\ominus}$ | 232 | 43100 | 5050 | 3·703 | 288 | 34720 | 14250 | 4·154 |

(*b*) The increase of the alkyl group in $\gamma$-position in the order Me → Et → iPr (2.1, 2.2 and 2·4) has the opposite effect; a pronounced effect on the *y* band ($\lambda_{max}$ and $\varepsilon_{max}$ increase sensibly) and a negligible effect on the *x* band ($\lambda_{max}$ is not affected, and $\varepsilon_{max}$ first increases, then decreases). These variations are indicated by the broken lines in Fig. 1.

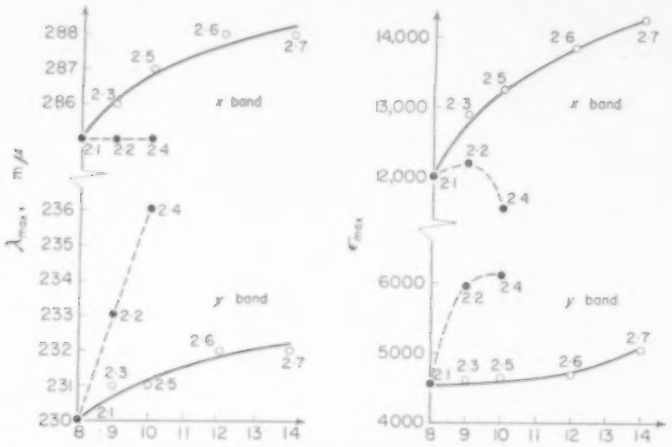



FIG. 1. Effect of alkyl groups. In abscissa, the number of carbon atoms in the formula.
—○— α positions; —●— — — γ position.

The variation of alkyl substituents in the order Me → Et → iPr → tBu has a bathochromic and hyperchromic effect on the *y* band when the substituent is in $\gamma$-position (broken lines are above full lines in Fig. 1 for the *y* band) and on the *x* band when the substituent is in α-position (full lines above broken lines in Fig. 1 for the *x* band).

TABLE 3. COLOUR AND FLUORESCENCE OF SOLUTIONS OF PHENYL-SUBSTITUTED PYRYLIUM PERCHLORATES

| Number of Ph-groups | Position | Colour | Fluorescence |
|---|---|---|---|
| 0 | — | colourless | no |
| 1 | $\gamma$ | colourless | violet, very slight |
| 1 | α | colourless | violet |
| 2 | α, $\gamma$ | colourless | blue |
| 2 | $\beta$, $\gamma$ | colourless | violet, slight |
| 2 | α, α | pale yellow | blue, strong |
| 3 | α, α, $\gamma$ | yellow | blue-green |
| 4 | α, α, $\beta$, $\gamma$ | pale yellow | green |

3. *The effect of phenyl groups* on the absorption spectra of pyrylium cations is much more pronounced than the effect of alkyl groups. This may be seen by the colour and fluorescence of the solutions (shown qualitatively in Table 3).

The absorption maxima are indicated in Table 4.

TABLE 4. ABSORPTION SPECTRA OF PYRYLIUM PERCHLORATES WITH ALKYL- AND PHENYL-SUBSTITUENTS (IX, X = $ClO_4$)

| No. | Substituents in IX | | | | Formula | No. of phenyl groups | | | | Solvent | Conc. (moles/l.) | x' Band | | | | y Band | | | | x Band | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | | α | β | γ | Total | | | $\lambda_{max}$ (mμ) | $\nu_{max}$ ($cm^{-1}$) | $\varepsilon_{max}$ | lg $\varepsilon_{max}$ | $\lambda_{max}$ (mμ) | $\nu_{max}$ ($cm^{-1}$) | $\varepsilon_{max}$ | lg $\varepsilon_{max}$ | $\lambda_{max}$ (mμ) | $\nu_{max}$ ($cm^{-1}$) | $\varepsilon_{max}$ | lg $\varepsilon_{max}$ |
| 4.1 | $CH_3$ | H | $CH_3$ | $CH_3$ | $C_8H_{11}O^{\oplus}$ $ClO_4^{\ominus}$ | 0 | 0 | 0 | 0 | 0·05 N $HClO_4$ | $10^{-2}$ | | | | | 230 | 43480 | 4550 | 3·658 | 285 | 35090 | 12000 | 4·079 |
| 4.2 | $CH_3$ | H | $CH_3$ | $C_6H_5$ | $C_{13}H_{13}O^{\oplus}$ $ClO_4^{\ominus}$ | 1 | 0 | 0 | 1 | 0·05 N $HClO_4$ | $5\cdot10^{-4}$ | 227 | 44050 | 11260 | 4·052 | 244 | 40980 | 10220 | 4·009 | 345 | 28990 | 24000 | 4·380 |
| 4.3 | $CH_3$ | H | $C_6H_5$ | $CH_3$ | $C_{13}H_{13}O^{\oplus}$ $ClO_4^{\ominus}$ | 0 | 0 | 1 | 1 | 0·05 N $HClO_4$ | $5\cdot10^{-4}$ | | | | | 304* | 32890 | 20000 | 4·301 | 327 | 30580 | 23400 | 4·369 |
| 4.4 | $C_6H_5$ | H | $C_6H_5$ | $CH_3$ | $C_{18}H_{15}O^{\oplus}$ $ClO_4^{\ominus}$ | 1 | 0 | 1 | 2 | 0·05 N $HClO_4$ | $5\cdot10^{-4}$ | 254 | 39370 | 14640 | 4·166 | 338 | 29590 | 23600 | 4·373 | 374 | 26740 | 29100 | 4·464 |
| 4.5 | $C_6H_5$ | H | $CH_3$ | $C_6H_5$ | $C_{18}H_{15}O^{\oplus}$ $ClO_4^{\ominus}$ | 2 | 0 | 0 | 2 | $CH_3COOH$ | $10^{-2}$ | 236 | 42370 | 13800 | 4·140 | 277 | 36100 | 18760 | 4·273 | 392 | 25510 | 26900 | 4·430 |
| 4·6 | $CH_3$ | $C_6H_5$ | $C_6H_5$ | $CH_3$ | $C_{19}H_{17}O^{\oplus}$ $ClO_4^{\ominus}$ | 0 | 1 | 1 | 2 | $CH_3COOH$ | $10^{-2}$ | | | | | 245 | 40820 | 8900 | 3·949 | 308 | 32470 | 11800 | 4·072 |
| 4.7 | $C_6H_5$ | H | $C_6H_5$ | $C_6H_5$ | $C_{23}H_{17}O^{\oplus}$ $ClO_4^{\ominus}$ | 2 | 0 | 1 | 3 | $CH_3COOH$ | $10^{-2}$ | 278 | 35970 | 18000 | 4·255 | 361† | 27700 | 30000 | 4·477 | 408† | 24510 | 24500 | 4·389 |
| 4.8 | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | $C_{28}H_{21}O^{\oplus}$ $ClO_4^{\ominus}$ | 2 | 1 | 1 | 4 | $CH_3COOH$ | $10^{-2}$ | 296 | 33780 | 17500 | 4·243 | 379 | 26380 | 20400 | 4·310 | 412 | 24270 | 19200 | 4·283 |

* Imprecise value: inflexion, the *x* and *y* bands are very near to one another, and partially overlapped.
† Literature values[6,7] 360 and 408 mμ.

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In order to study systematically the effect of phenyl groups, absorption spectra have been determined for all six possible compounds having methyl and/or phenyl groups in the 2,4 and 6 positions (4.1, 4.2, 4.3, 4.4, 4.5 and 4.7) and for compounds containing a phenyl group in $\beta$ position (4.6 and 4.8). For comparison purposes, the spectrum of 2,4,6-trimethylpyrylium perchlorate has been included also in Table 4 (1.4 = 2.1 = 4.1).

To observe the effect of phenyl groups, Fig. 2 represents the data from Table 4.

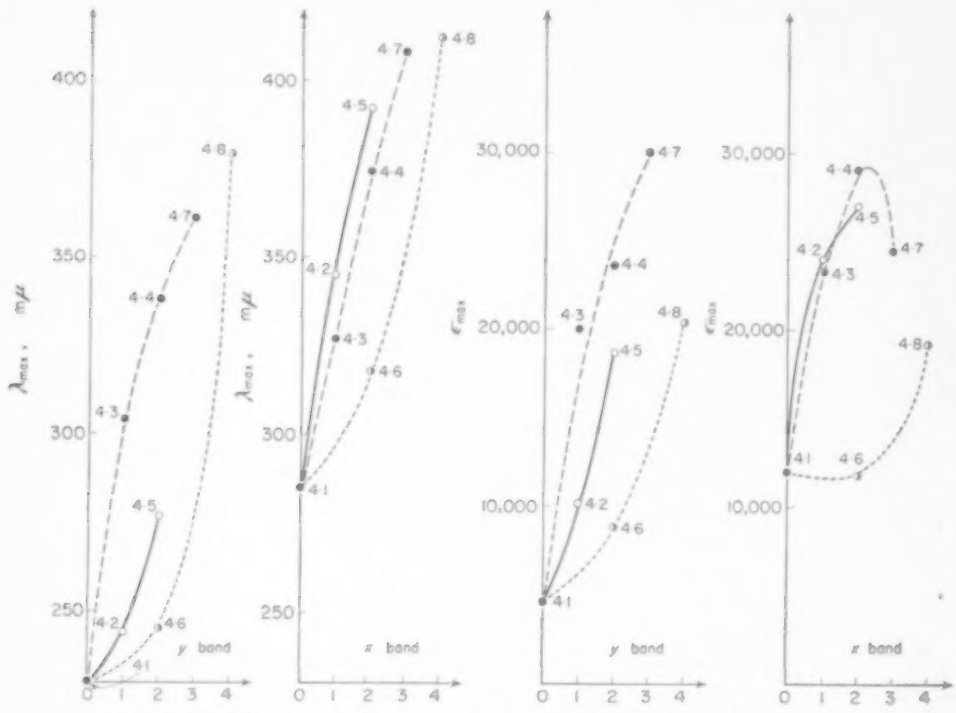


FIG. 2. Effect of phenyl groups. In abscissa, the number of phenyl groups.
—○— $\alpha$ positions; —●— — — $\gamma$ position; .◑. . . . $\beta$ position.

The following general remarks may be made:

(*a*) Phenyl groups cause batho- and hyper-chromic effects which are much larger than those due to alkyl groups: while the latter are less than 10 m$\mu$ (for $\lambda_{max}$) and 30 per cent (for $\varepsilon_{max}$), the former are about 100 m$\mu$ and 300 per cent. This is easy to explain, taking into account that aryl groups may stabilize more effectively, through electronic effects, the positive charges in $\alpha$ and $\gamma$ positions (VIII, R = Ar) than alkyl groups through their inductive effects. It must be emphasized that these large influences of the phenyl groups on the spectrum of the pyrylium nucleus arise only from phenyl–pyrylium, and not from phenyl–phenyl interactions, since the phenyl groups in the 2,4 and 6 positions are mutually in *meta* position, and it is established[14] that in the *m*-polyphenyl series, only $\varepsilon_{max}$ and not $\lambda_{max}$ is increasing

[14] A. E. Gillam and D. H. Hey, *J. Chem. Soc.* 1170 (1930); A. E. Gillam and E. S. Stern, *An Introduction to Electron Absorption Spectroscopy in Organic Chemistry*. Arnold, London (1954); J. N. Murrell and H. C. Longuet-Higgins, *J. Chem. Soc.* 2552 (1955).

with the number of phenyl groups. The sole cases when an interaction between two phenyl groups is plausible are those with two phenyl groups in *ortho* to one another (4.6 and 4.8), when both electronic and steric effects are probably involved (these cases have therefore been separately represented by broken lines in Fig. 2).

(*b*) Because of the different orders of magnitude alkyl effects may be neglected as a first approximation relative to phenyl effects.

(*c*) Phenyl groups in $\alpha$ positions (4.1, 4.2 and 4.5) have a bathochromic effect which is greater for the *x* band than for the *y* band, just as in the case of alkyl groups (full lines in Fig. 2).

(*d*) Phenyl groups in $\gamma$ positions (4.1, 4.3, 4.4 and 4.7) have a batho- and hyperchromic effect which is greater for the *y* band than for the *x* band, just as in the case of alkyl groups (broken lines in Fig. 2).

(*e*) The introduction of a phenyl group in $\beta$ position besides a $\gamma$-phenyl group (4.6 and 4.8) has a smaller effect than the two preceding ones, and the *x* and *y* bands behave similarly.

(*f*) When there are one or two phenyl groups in $\alpha$-position, a third band appears in the experimentally accessible spectral region (designated *x'* band in Table 4). It is influenced by phenyl groups similarly to the *x* band, but no conclusions can be drawn until the $\lambda_{max}$ and $\varepsilon_{max}$ will be known for this *x'* band in the whole series.

(*g*) While in the alkyl-substituted series the *x* band presented an absorption coefficient $\varepsilon_{max}$ 2–3 times greater than the *y* band, in the phenyl-substituted series, especially when a $\gamma$-phenyl is present, $\varepsilon_{max}$ values become comparable for the *x* and *y* bands and for the last two compounds in Table 4 (4.7 and 4.8) the absorption intensity is greater for the *y* band than for the *x* band. This is to be expected in view of the different effects of phenyl groups on the *x* and *y* bands. These different effects are responsible for the appearance of the *y* band for 4.3 as a shoulder (inflexion) on the ascending branch of the absorption curve.

(*h*) The only exception to the rule that phenyl groups cause bathochromic and hyperchromic effects, is the hypochromic effect observed for the *x* band when the substituent is in $\gamma$-position. The same exception may be observed in the alkyl-substituted series (Figs. 1 and 2, $\varepsilon_{max}$ for the *x* band, broken lines).

The qualitative conclusions are similar to those from the case of alkyl derivatives: increasing the number of phenyl groups generally causes a batho- and hyper-chromic effect, but this is more pronounced for the *y* band when the $\gamma$ position is involved (broken lines are above full lines for the *y* band in Fig. 2) and for the *x* band when $\alpha$-positions are involved (full lines above broken lines for the *x* band in Fig. 2). Phenyl groups in $\beta$ exert a smaller influence.

The data published by Wizinger and Ulrich[7] relative to 2,4,6-triphenyl-substituted pyrylium perchlorates with $NMe_2$ and/or OMe auxochromic groups in the *para* positions of the phenyl groups bear out these conclusions, though the comparison can be made only for $\lambda_{max}$ of the *x* band.

The data reproduced in Table 5 refer to acetic acid solution.

In Fig. 3 the wavelengths have been represented as function of the number of auxochromic groups in the same way as in Figs. 1 and 2, using Wizinger and Ulrich's data. Each point in Fig. 3 is numbered as in Table 5.

It may be observed that again increasing the number of auxochromic groups leads to bathochromic shifts which are greater when $\alpha$-positions are involved (full lines

are above broken lines in Fig. 3). A hypsochromic effect is evident for the compound with three $NMe_2$ groups (see above under *h*). It is apparent that *p*-methoxyphenyl,

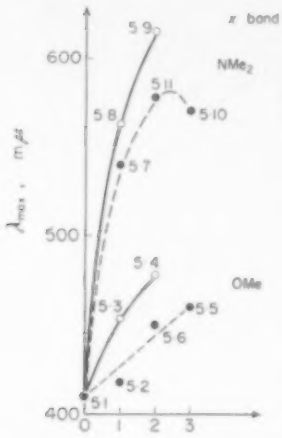


FIG. 3. Effect of auxochromic groups. In abscissa, the number of auxochromic groups. —○— α positions; —●— γ position.

TABLE 5. ABSORPTION SPECTRA OF 2,4,6-TRIPHENYLPYRYLIUM PERCHLORATES WITH AUXOCHROMES IN *para*-POSITIONS AFTER WIZINGER AND ULRICH[7]

| No. | Notation in Wizinger and Ulrich's paper[7] | Substituents in *para*-positions of the phenyl groups | | | *y* band | *x* band |
|---|---|---|---|---|---|---|
| | | 2 | 4 | 6 | $\lambda_{max}$ (mμ) | $\lambda_{max}$ (mμ) |
| 5.1 | Ic | H | H | H | 360 | ca. 408 |
| 5.2 | IIc | H | OMe | H | | 418 |
| 5.3 | IIIc | H | H | OMe | | 454 |
| 5.4 | IVc | OMe | H | OMe | | 478 |
| 5.5 | Vc | OMe | OMe | OMe | 420 | ca. 460 |
| 5.6 | VIc | H | OMe | OMe | 416 | ca. 450 |
| 5.7 | VIIc | H | $NMe_2$ | H | | 540 |
| 5.8 | VIIIc | H | H | $NMe_2$ | | 563 |
| 5.9 | IXc | $NMe_2$ | H | $NMe_2$ | | 615 |
| 5.10 | Xc | $NMe_2$ | $NMe_2$ | $NMe_2$ | 533 | ca. 570 |
| 5.11 | XIc | H | $NMe_2$ | $NMe_2$ | | 578 |

and even more *p*-dimethylaminophenyl, groups may stabilize more effectively positive charges than do phenyl groups.

*Discussion of the results*

No evidence has been obtained in favour of hyperconjugation in the series of alkyl-substituted pyrylium salts.[15]

The three bands found in the absorption spectrum of pyrylium salts VI are clearly related to the bands in the spectrum of benzene III, pyridine IV, and pyridinium compounds V. Two facts are apparent. Firstly, the vibrational structure of the bands, manifest for III is less pronounced for IV,[16] still less for V (for instance, the U.V. spectrum of pyridine-N-oxide has no vibrational structure[17]), and completely vanishes for VI. Apparently, the absence of vibrational structure in the spectra of pyrylium salts is not therefore attributable to the polar solvents employed, but is intimately associated with the absorbent cation (probably it is not due to a loose-bolt effect, since these cations are strongly fluorescent).

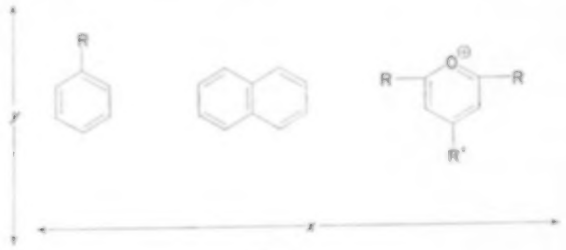


FIG. 4.

Secondly, the absorption intensities show a regular trend in the series III–VI: as the electronegativity of the heteroatom increases, the forbiddeness of the $\pi$–$\pi^*$ transitions decreases, so that the absorption intensities are considerably changed. In the case of trimethylpyrylium perchlorate in 0·05 N perchloric acid, the oscillator strength values $f$ are about 0·175 for the $x$ band and 0·043 for the $y$ band.

Thus, neither vibrational structure, nor absorption intensity can help in establishing relationships between the absorption spectra of compounds III–VI; this must be done only on the basis of sequence of bands in the spectrum and effect of substituents. But these two latter factors are consistent with one another as shown in the following.

Judging from the sequence of bands, the $x$ band with longest wavelength is related to the $^1A_{1g}$–$^1B_{2u}$ $\pi$–$\pi^*$ singlet transition in the benzene spectrum (Platt symbol: $^1L_b$[18]; Clar symbol: $\alpha$ band[19]; Moffit symbol: $V$[20]), the $y$ band is related to the $^1A_{1g}$–$^1B_{1u}$ $\pi$–$\pi^*$ singlet transition in the benzene spectrum (Platt symbol: $^1L_a$; Clar symbol: $p$ band; Moffit symbol: $U$) and the $x'$ band which is shifted

[15] M. J. S. Dewar and A. N. Schmeising, *Tetrahedron* **5**, 166 (1959).
[16] cf. F. Matsen, *Chemical Applications of Spectroscopy* (Edited by F. West) pp. 629–706. Interscience, New York (1956); H. A. Staab, *Einführung in die theoretische organische Chemie* pp. 292–419. Verlag Chemie, Weinheim (1959).
[17] H. H. Jaffé, *J. Amer. Chem. Soc.* **77**, 4451 (1957); M. Ito and W. Mizushima, *J. Chem. Phys.* **24**, 495 (1956).
[18] J. R. Platt, *J. Chem. Phys.* **17**, 484 (1949); **19**, 101 (1951).
[19] E. Clar, *Aromatische Kohlenwasserstoffe* (2nd Ed.) p. 36. Springer, Berlin (1952); *Chem. Ber.* **82**, 495 (1949).
[20] W. Moffitt, *J. Chem. Phys.* **22**, 320 (1954).

into the accesible ultra-violet region only in a few pyrylium salts is related to the $^1A_{1g}$–$^1E_{1u}$ $\pi$–$\pi^*$ singlet transition in the benzene spectrum (Platt symbol: $^1B$; Clar symbol: $\beta$ band; Moffitt symbol: $X$, $Y$). This $x'$ band is expected to be followed by another band at shorter wavelengths, which should be called $y'$ band: then the $x'$ band should correspond to the $^1B_b$ or $\beta$ band, and the $y'$ band to the $^1B_a$ or $\beta'$ band in the spectrum of aromatic compounds.†

This assignment leads to the prediction that the $x$ and $x'$ bands must be polarized in the $x$ direction (Fig. 4), having a nodal line through the heteroatom, while the $y$ (and the predicted $y'$) bands must be polarized in the $y$ direction, having a nodal line between the atoms.[18]

(The notations $x$, $x'$, $y$ and $y'$ have been chosen to emphasize the relationship with other bidimensional molecules with mobile $\pi$-electrons[21]).

TABLE 6. COMPARISON OF SPECTRA OF SYM-TRIMETHYL-DERIVATIVES OF COMPOUNDS III–VI

| | $y$ Band | | $x$ Band | |
|---|---|---|---|---|
| | $\lambda_{max}$ (m$\mu$) | $\varepsilon_{max}$ | $\lambda_{max}$ (m$\mu$) | $\varepsilon_{max}$ |
| Mesitylene[22] | 215 | 7420 | 265[a] | 219[a] |
| sym-Collidine[23] | ca. 216 | 6900 | 267 | 4000 |
| 1,2,4,6-Tetramethylpyridinium perchlorate[b] | 221 | 5100 | 268 | 7340 |
| 2,4,6-Trimethylpyrylium perchlorate[b] | 230 | 4550 | 285 | 12000 |

[a] Main vibrational peak
[b] Present work

This prediction is borne out by the effect of substituents: the $x$ and $x'$ bands are influenced by substituents in $\alpha$ and $\alpha'$ positions, while the $y$ band is influenced by substituents in $\gamma$ position. One could assume that in the first and third electronically excited state of the pyrylium cation, structures VIIIc + VIIId are contributing more than in the ground state, while in the second excited state structure VIIIe is contributing more‡.

Comparison between the absorption spectra of mesitylene,[22] collidine [23] and trimethylpyrylium perchlorate is also instructive, and we recorded the spectrum of

† See V. Burawoy and J. P. Critchley, *Tetrahedron* **5**, 340 (1959) for a different assignment of the $p$ and $\beta$ bands in the benzene spectrum.

‡ This is a possible explanation of the specific reaction of pyrylium compounds with nucleophilic reagents in $\alpha$-positions, since the first electronically excited state of the molecule (responsible for the $x$ band) is somewhat associated with the presence of positive charges in $\alpha$-positions. Alternative explanations are the presence of two structures with positive charge in $\alpha$ (VIIIc and VIIId) and only one structure for $\gamma$ position (VIIIe), or the smaller charge separation in the former than in the latter.

[21] G. N. Lewis and M. Calvin, *Chem. Rev.* **25**, 273 (1939); G. N. Lewis and J. Bigeleisen, *J. Amer. Chem. Soc.* **65**, 2102, 2107 (1943); W. D. Kumler, *J. Amer. Chem. Soc.* **68**, 1104 (1946); R. N. Jones, *Chem. Rev.* **41**, 353 (1947).

[22] E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.* **71**, 2932 (1949); C. W. Rector, G. W. Schaeffer and J. R. Platt, *J. Chem. Phys.* **17**, 460 (1949).

[23] N. Ikekawa, N. Maruyama and Y. Sato, *Pharm. Bull. Japan* **2**, 209 (1954); D. Rostafinska, *Roczn. Chem.* **29**, 803 (1955).

1,2,4,6-tetramethylpyridinium perchlorate in 0·05 N $HClO_4$ ($10^{-3}$ molar solution). The results are summarized in Table 6.

It is apparent that with increasing electronegativity of the heteroatom in the sequence mesitylene → collidine → N-methyl-collidinium → trimethylpyrylium both the *x* and *y* bands are shifted towards longer wavelengths, that $\varepsilon$ decreases for the *y* band and strongly increases for the *x* band, and that the last two compounds are completely devoid of vibrational structure.

## EXPERIMENTAL

A CΦ4 spectrophotometer was employed. All pyrylium compounds mentioned were prepared as described,[9] with the exception of 2,4-diphenyl-6-methylpyrylium perchlorate (4·4) which was obtained according to Diels and Alder.[26] Pyrylium perchlorates with alkyl substituents or with one phenyl group were purified by recrystallization from aqueous 0·05 N perchloric acid. Pyrylium perchlorates with two or more phenyl groups were recrystallized from acetic acid. Commercial reagents and solvents were employed, without further purification.

1,2,4,6-Tetramethylpyrydinium perchlorate was prepared from 2,4,6-trimethylpyrylium perchlorate and methyl amine and had m.p. 204–205° (uncorr.) from water: literature values m.p. 206–207°[25], 202°[26], 201°[27].

*Acknowledgement*—We wish to thank Professor C. D. Nenitzescu for stimulating discussions.

[26] O. Diels and K. Alder, *Ber. Dtsch. Chem. Ges.* **60**, 716 (1927).
[25] A. Baeyer and J. Piccard, *Liebigs Ann.* **384**, 208 (1911).
[26] E. Weitz and T. Konig, *Ber. Dtsch. Chem. Ges.* **55**, 2864 (1922).
[27] B. Emmert and O. Varenkamp, *Ber. Dtsch. Chem. Ges.* **56**, 491 (1923).

Tetrahedron, 1960. Vol. 9, pp. 175 to 182. Pergamon Press Ltd. Printed in Northern Ireland

# 2-ARYL-4-METHYL-4-CHLOROCARBONYL-OXYMETHYL-2-OXAZOLINES

## CHEMICAL REACTIVITY AND INFRA-RED SPECTRA

V. ROSNATI and D. MISITI
Istituto Superiore di Sanità, Roma, Italia

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**Abstract**—2-Aryl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazolines have been shown to exhibit a particular reactivity towards nucleophilic reagents. This reactivity is to be attributed to the presence of the chlorocarbonic ester function. Reaction of the above 2-oxazolines with ammonia (or dimethylamine) results in ring opening, with the formation of benzamide (or N,N-dimethyl-benzamide) and 4-methyl-4-chloromethyl-oxazolidin-2-one (or 4-methyl-4-N,N-dimethylaminomethyl-oxazolidin-2-one). The presence of the chlorocarbonic ester function also affects the position of the C=N band in the infra-red spectrum of these 2-oxazoline derivatives; this band is shifted approximately 40 $cm^{-1}$ towards lower wavelengths in comparison with the absorption band of structurally related compounds which do not possess the chlorocarbonic ester group. A possible reaction mechanism is proposed together with a correlation of the chemical and spectroscopical findings.

2-ARYL-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazolines (I) are stable, crystalline compounds. The presence of a chlorocarbonate group, however, confers on these oxazoline a rather remarkable chemical reactivity.

As previously reported,[1] these chlorocarbonates on heating with water undergo a complex reaction, giving the corresponding 4-methyl-4-aroyl-oxymethyl-oxazolidin-2-one (II).

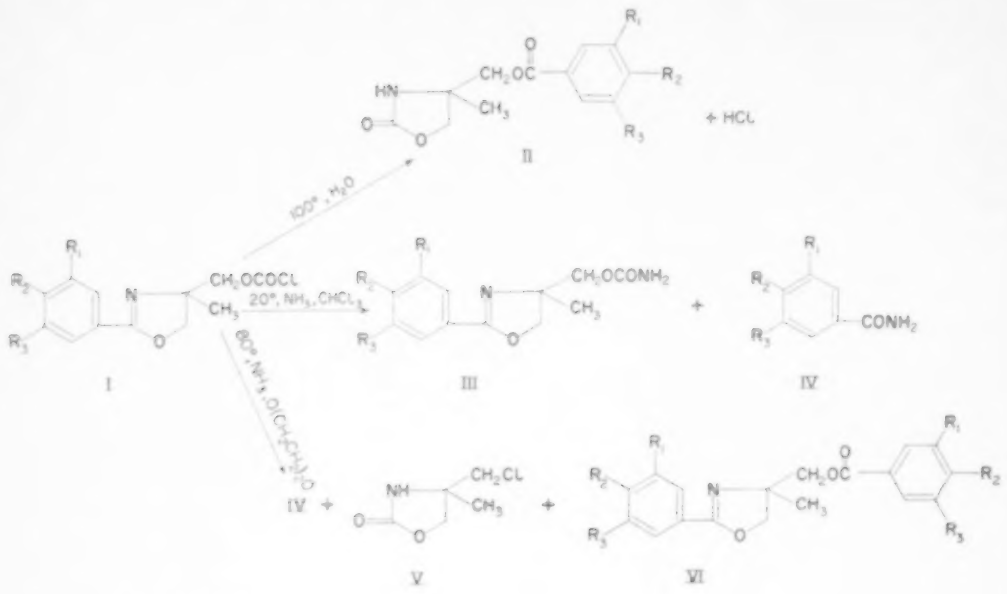
While in the above reaction no fragmentation occurs except for the splitting of one mole of hydrogen chloride, the action of cold aqueous ammonia or dimethylamine results in the degradation of the oxazoline ring, benzamide or N,N-dimethyl-benzamide having been obtained quantitatively.

Under anhydrous conditions, carbamates (III) are obtained if the chlorocarbonates (I) react for long time at room temperature with a small excess of ammonia.[2] However, even under these mild conditions, a partial attack on the oxazoline ring occurs. In the case of the 2-*p*-chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline (Ib), careful chromatographic separation showed that *p*-chlorobenzamide is present in small quantities, together with the corresponding carbamate (IIIb) and about 50 per cent of the unreacted starting material.

The course of the reaction, and consequently, the yield of the different carbamates, seem to depend on ammonia concentration and reaction time, rather than on temperature.

The relative stability of these chlorocarbonates towards nucleophilic reagents seems also to depend on the substituents in the benzene ring. When compound Ib reacts with excess ammonia under anhydrous conditions, the corresponding carbamate (IIIb) is formed in 50 per cent yield. On the contrary, chlorocarbonate (Ic)

[1] V. Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 162 (1960).
[2] V. Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 171 (1960).



Ia, IIa, IIIa, IVa, VIa: $R_1, R_2, R_3 = H$
Ib, IIb, IIIb, IVb, VIb: $R_1, R_3 = H$ $R_2 = Cl$
Ic, IIc, IIIc IVc : $R_1, R_2, R_3 = OCH_3$

under similar conditions yields no carbamate but instead 3,4,5-trimethoxy-benzamide is obtained quantitatively.

As the formation of benzamide or substituted benzamides accounts for only a part of the total chlorocarbonate, a careful study resulted in the isolation of other products and led to a theory of a possible reaction mechanism.

The chlorocarbonates Ia, Ib, Ic when treated with a large excess of ammonia in anhydrous dioxane, undergo complete degradation of the oxazoline ring, yielding in all cases benzamide (or substituted benzamides) and a new compound $C_5H_8ClNO_2$.

The latter compound is neutral with the chlorine easily removable by treatment with alkaline carbonates. Its infra-red spectrum shows a strong band at 1764 $cm^{-1}$ (suggesting the presence of a carbonyl group in a five-membered lactone ring) and a weak band at 3484 $cm^{-1}$, in the region of the N—H absorption. On the basis of chemical and spectroscopical data, compound $C_5H_8ClNO_2$ was identified as 4-methyl-4-chloromethyl-oxazolidin-2-one (V), not yet described in the literature.

The assignment of structure V to compound $C_5H_8ClNO_2$ was confirmed by its synthesis through chlorination of known 4-methyl-4-hydroxy-methyl-oxazolidin-2-one with thionyl chloride.

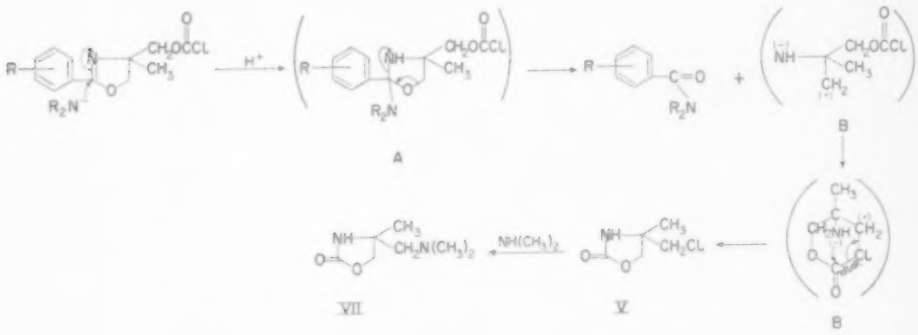
In the case of chlorocarbonate Ib, in addition to compound $C_5H_8ClNO_2$, another product of empirical formula $C_{18}H_{15}Cl_2NO_3$ was isolated, but in very small amount. This compound is neutral with the chlorine atoms unaffected by alkaline treatment. Its infra-red spectrum shows a strong band at 1733 $cm^{-1}$, indicative of an aryl ester function, and another strong band at 1653 $cm^{-1}$, which is attributed to the C=N stretching vibration of a 2-oxazoline ring. On this basis compound $C_{18}H_{15}Cl_2NO_3$ was identified as 2-*p*-chlorophenyl-4-methyl-4-*p*-chlorobenzoyl-oxymethyl-2-oxazoline

(VIb). Final confirmation was obtained by esterification of 2-*p*-chlorophenyl-4-methyl-4-hydroxymethyl-2-oxazoline to VIb.

The nucleophilic attack on these oxazoline chlorocarbonates was also carried with dimethylamine to determine whether the nitrogen atom in compound V was the one originally incorporated in the oxazoline ring or whether it came from the ammonia. From the reaction of 2-*p*-chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline (Ib) and dimethylamine, *p*-chloro-N,N-dimethyl-benzamide was isolated together with a new compound $C_7H_{14}N_2O_2$, which, on the basis of spectroscopical data, was identified as a derivative of compound V, namely 4-methyl-4-N,N-dimethyl-aminomethyl-oxazolidin-2-one (VII). This same compound VII was obtained directly by reaction of dimethylamine with the intermediate V.

The importance of the chlorocarbonic group in determining the oxazoline ring opening is fully illustrated by the fact that 2-*p*-chloromethyl-phenyl-2-oxazoline is converted, by excess diethylamine at 100°, to 2-*p*-diethylaminomethyl-phenyl-2-oxazoline, the oxazoline ring remaining intact.[3]

The following scheme summarizes the above findings and the proposed reaction mechanism:




According to this scheme, the first step of the reaction between chlorocarbonate (I) and ammonia (or dimethylamine) can be visualized as an addition of the nucleophilic reagent to the carbon–nitrogen double bond of the oxazoline ring. The nucleophilic attack should be initiated by an anion $R_2N^-$ attack on carbon atom in position 2 of the ring, where an electron deficiency exists, owing to the proximity of a benzene ring, and two atoms possessing high electron affinity.

The postulated intermediate A, by means of the indicated electron shifts, clearly accounts for the formation of benzamide, or substituted benzamides.

The zwitterion B could also be formed, and, through a concerted mechanism involving migration of the chlorine atom and formation of a new carbon–nitrogen bond, compound V could be formed.

The infra-red absorption spectra offer a rational interpretation of the chemical reactivity of these 2-oxazoline chlorocarbonates. Thus, oxazoline derivatives of type VIII, which are stable towards nucleophilic reagents, regularly show the C=N absorption bond between 1653 and 1647 $cm^{-1}$, depending on the substituents on the

[3] M. T. Leffler and R. Adams, *J. Amer. Chem. Soc.* **59**, 2252 (1937).

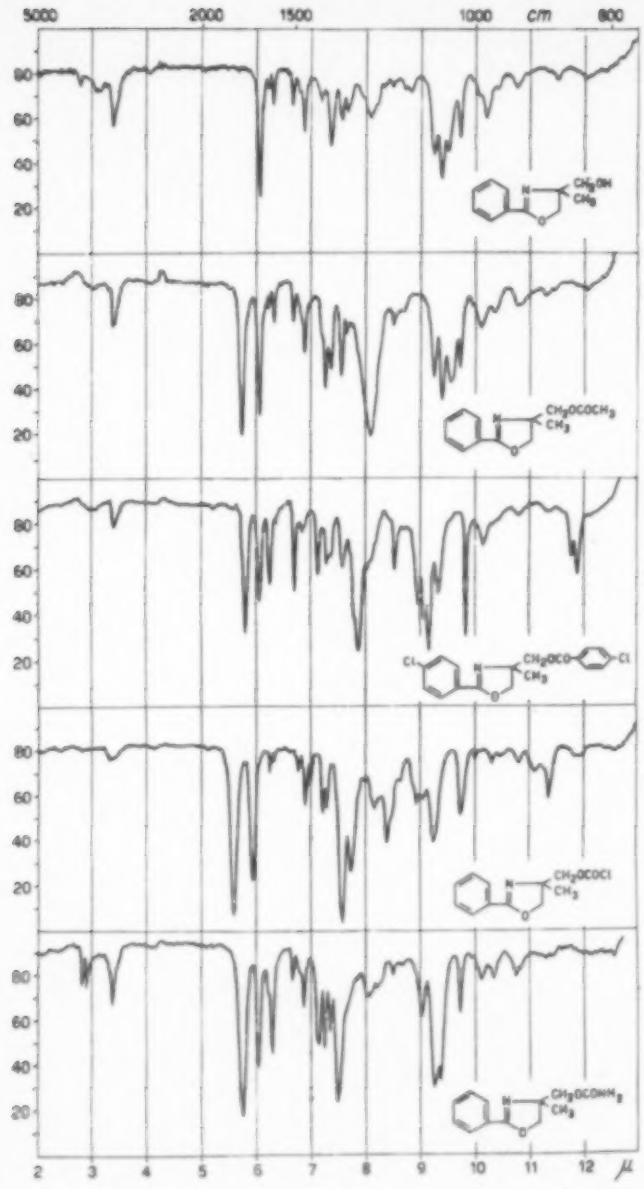


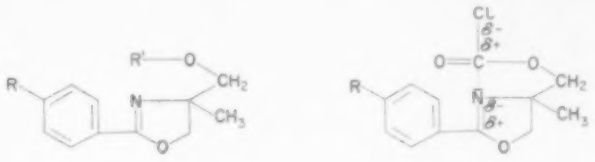

FIG. 1.

benzene ring (Fig. 1). These values are in good agreement with those reported in the literature.[4]

Instead, chlorocarbonates (I) show in their infra-red spectra two strong bands in the carbonyl region: one is constantly at 1795 $cm^{-1}$ and it is due to the C=O

[4] R. B. Barnes, R. C. Gore, U. Liddel and W. Van Zandt, *Infra-red Spectroscopy*. Reinhold, New York (1944); L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 227. Methuen, London (1956).

vibration of the chlorocarbonate moiety;[5] the other band, which is in the region between 1692 and 1686 $cm^{-1}$ depending on the substituents in the benzene ring, is attributed to the C=N stretching vibration of the oxazoline ring. Therefore chlorocarbonates (I), which are unstable towards nucleophilic reagents, show the absorption band of the C=N group at frequencies increased by approximately 40 $cm^{-1}$. These facts may depend on the effect of the chlorocarbonic group on the carbon–nitrogen double bond in the ring: the relative spatial interaction of these two groups could account for both the chemical and spectroscopical properties of these chlorocarbonates. Formula IX may well visualize the actual interaction of the two groups, the highly polarized carbon–chlorine bond being responsible of the induced polarization of the neighbouring C=N double bond.



VIII IX

R=H; Cl; R'=H; $COCH_3$, $COC_6H_5$, $COC_6H_4$—pCl, $CONH_2$.

According to this view, the polarization of the carbon–nitrogen double bond must be considered the driving force of the process which ultimately leads to the ring opening.

At the same time, the increased polarization of the carbon–nitrogen double bond may well account, in these chlorocarbonates, for the observed shift of the C=N band towards shorter wavelengths. Structure IX could also explain the experimental finding that these chlorocarbonates do not give the corresponding hydrochlorides when treated with dry hydrochloric acid in anhydrous chloroform solution: in fact the nitrogen electron pair, which normally participates in the salt formation, is here partially screened off from the approaching proton.

On the contrary, compound of type VIII, under similar conditions, give stable, crystalline hydrochlorides.[2,6]

## EXPERIMENTAL*

*Reaction between 2-phenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline* (Ia) *and ammonia.* Compound Ia (3·3 g) was heated in a sealed tube for 24 hr at 80° with a saturated solution of anhydrous ammonia in dry dioxane (150 cc). After filtration and removal of solvent (red press), the residue was treated with cold, dry benzene, leaving a residue. The latter after recrystallization from benzene, yielded 1·2 g of crystals (m.p. 127–129°). Found: C, 69·59; H, 6·09; N, 11·66. $C_7H_7NO$ requires: C, 69·40; H, 5·83; N, 11·56%). This product was identified by mixed melting point and infra-red

* Melting and boiling points are uncorrected. Elementary micro-analyses were carried out by Dr. M. Marzadro and Dr. A. M. Pirelli of the Micro-analysis Laboratory of the Istituto Superiore di Sanità, Rome. Infra-red absorption spectra were recorded for all the substances described on a Perkin Elmer 21 spectrophotometer.

[5] This value is in good agreement with those reported in the literature, although no detailed information is available concerning the infra-red absorption of different chlorocarbonates. H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, *Infra-red Determination of Organic Structures*. Van Nostrand, New York (1949) have given a value of 1785 $cm^{-1}$ for ethyl chlorocarbonate. N. B. Colthup, *J. Opt. Soc. Amer.* **40**, 397 (1950) quotes a range of 1790–1770 $cm^{-1}$ based on this unpublished work.

[6] V Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 155 (1960).

spectrum as benzamide. The remaining benzene solution, after removal of the solvent at reduced pressure, gave an oily residue (2·3 g), which was dissolved in a mixture (75 cc) of benzene–petrol ether 4:1. This solution was fractioned using an alumina column 11 cm high and 3 cm in diameter (20 g alumina). Fractions 1 to 4 inclusive (75 cc each) were eluted with a 1:1 benzene–petrol ether solution and yielded 80–90 mg of an oil, which, on the basis of infra-red spectra, appeared to be a mixture of the cyclic urethane (V), the predominant component, and a 2-oxazoline derivative having an aromatic ester function.*

The latter compound was not easily separable either by chomatography or fractional distillation; thus, the 2-oxazoline derivatives (presumably the ester VIa) could not be isolated in a pure state. Fractions 5–14 (75 cc each) were eluted with benzene and gave a colourless oil (1·1 g), which was fractionated at low pressure.

A small quantity of a white crystalline product (m.p. 127–129°, b.p. 110–115° at 0·1 mm) was obtained in the first fraction; this was identified as benzamide by its mixed melting point and infra-red spectrum. The main portion of the distillation product was a colourless oil b.p. 135–140° at 0·1 mm, which on standing formed crystals m.p. 75–85°. After repeated recrystallizations from benzene–petrol ether, the m.p. was raised to 89–91°. (Found: C, 40·33; H, 5·33; N, 9·55; Cl, 23·50. $C_5H_8ClNO_2$ requires: C, 40·15; H, 5·39; N, 9·36; Cl, 23·72%). These crystals showed no depression on admixture with authentic 4-methyl-4-chloromethyl-oxazolidin-2-one (V) prepared as described below. The infra-red spectra of both these samples were also identical.

*4-Methyl-4-chloromethyl-oxazolidin-2-one* (V). 4-Methyl-4-hydroxymethyl-oxazolidin-2-one[3] (7 g) suspended in anhydrous chloroform (50 cc) was treated with thionyl chloride (20 cc) and the reaction mixture allowed to stand at room temp until solution was complete and then refluxed for 4 hr. Chloroform and thionyl chloride were removed at reduced pressure and the residue (8 g) was fractionated *in vacuo*. The first fraction (4 g) was collected between 138–144° at 0·1 mm; the remainder of the distillate (1·5 g), (b.p. 166–172° at 0·1 mm) consisted of unreacted starting material (m.p. 115–117° and identical infra-red spectrum). After redistillation, the first fraction gave colourless oil (b.p. 135–136° at 0·1 mm) which on standing solidified completely (m.p. 75–86°). Repeated recrystallization from benzene–petrol ether gave pure crystals of V, m.p. 90–92°. (Found: C, 40·14; H, 5·41; N, 9·14; Cl, 23·68. $C_5H_8ClNO_2$ requires: C, 40·15; H, 5·39; N, 9·36; Cl, 23·72%). Infra-red absorption ($CHCl_3$): 3472 (w), 3263 (w), 1773 (s), 1761 (s), 1381 (m) $cm^{-1}$.

*Reaction between 2-p chlorophenyl-4-methyl-4-chlorocarbonyl-oximethyl-2-oxazoline* (Ib) *and ammonia*. A solution of a compound Ib (1·3 g) in dry dioxane (50cc) was saturated at room temp with anhydrous ammonia and the reaction mixture was heated at 80° for 12 hr in a sealed tube. After removal of the solvent (red press) the crystalline residue was dissolved in the least quantity of hot benzene. Upon standing, crystals (0·3 g, m.p. 179–180°) were obtained. Found: C, 53·90; H, 4·06; N, 8·93; Cl, 22·72. $C_7H_6NOCl$ requires: C, 54·03; H, 3·89; N, 9·00; Cl, 22·79%). This product was identified by mixed melting point and infra-red spectrum as *p*-chlorobenzamide. The remaining benzene solution, after removal of the solvent (red press) gave an oily residue (0·6 g) which was dissolved in benzene–petrol ether 3:1 (25 cc) and chromatographed over alumina (21 g). Elution was carried out with benzene–petrol ether 3:1. The first three fractions (25 cc each) yielded 0·1 g (VIb), m.p. 122–123° (from petrol ether). (Found: C, 59·23; H, 4·17; N, 3·91; Cl, 19·30. $C_{14}H_{13}Cl_2NO_3$ requires: C, 59·35; H, 4·15; N, 3·85; Cl, 19·47%). This product showed no depression of the m.p. with VIb prepared as described below. The infra-red spectra of both materials were also identical. Subsequent fractions (4–11) afforded 0·5 g of a crystalline compound m.p. 87–93°. Crystallization from benzene–petrol ether gave needles of V with m.p. 90–92°. (Found: C, 40·15; H, 5·52; N, 9·46; N, 9·46; Cl, 23·49. $C_5H_8ClNO_2$ requires: C, 40·14; H, 5.52; N, 9·37; Cl, 23·70%). The c ystals m.p. 90–92° were not depressed upon admixture with V prepared as described above. The infra-red spectra of both these compounds were identical.

*Reaction between 2-p-chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline* (Ib) *and dimethylamine*. A solution of compound Ib (4 g) and anhydrous dimethylamine (12 g) in dry dioxane (100 cc) was heated in a sealed tube for 24 hr at 80–85°. After filtration and removal of the solvent

* Infra-red spectra of these fractions showed two strong bands in the region of the carbonyl: one at 1770 (s) $cm^{-1}$, which can be attributed to the carbonyl of the cyclic urethane (V) and the other at 1733 (s) $cm^{-1}$, suggesting the presence of an aromatic ester function. Further evidence for the presence of a benzene ring is given by two bands at 1610 (w) $cm^{-1}$ and 1499 (w) $cm^{-1}$. The appearance of a strong band at 1653 (s) $cm^{-1}$ clearly indicates the presence of an oxazoline ring.

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(red press), the residue was dissolved in benzene–petrol ether 1:1 (30 cc) and the solution chromatographed over alumina (120 g). The first seven fractions (100 cc each; elution with benzene–petrol ether 1:1) gave an oily material which solidified upon standing; the crude product (2 g; m.p. 50–55°), after crystallization from benzene–petrol ether, gave crystals m.p. 56–58°. (Found: C, 58·63; H, 5·51; N, 7·76; Cl, 19·20. $C_9H_{10}ClNO$ requires: C, 58·86; H, 5·49; N, 7·63; Cl, 19·31%). This product was identified by mixed m.p. and infra-red spectrum as 4-chloro-N,N-dimethyl-benzamide. Subsequent fractions (eluted with benzene and benzene–ether 1:1) gave a colourless oil (2 g) which, after distillation *in vacuo*, gave 1·7 g (VII), b.p. 69–73° at 0.03 mm. After long standing, crystals m.p. 55–59° were obtained. (Found: C, 53·13; H, 8·91; N, 17·69. $C_7H_{14}N_2O_2$ requires: C, 53·14; H, 8·92; N, 17·71%). The I.R. spectrum of this compound was identical to that obtained with VII prepared as described below.

4-*Methyl*-4-N,N-*dimethylaminomethyl-oxazolidin*-2-*one* (VII). A solution of V (3 g) and anhydrous dimethylamine (7 g) in dry dioxane (100 cc) was heated in a sealed tube for 24 hr at 80–85°. After filtration and removal of the solvent (red press) the oily residue was fractionated *in vacuo*. Compound VII was thus obtained as a colourless oil (2·3 g; b.p. 70–74° at 0·03 mm) which after long standing solidified completely, giving crystals m.p. 54–59°. (Found: C, 52·89; H, 9·12; N, 17·44. $C_7H_{14}N_2O_2$ requires: C, 53·14; H, 8·92; N, 17·71%). Infra-red absorption ($CHCl_3$): 3333 (w) broad, 1764 (w), 1664 (s), 1653 (s), 1412 (m) $cm^{-1}$.

2-p-*Chlorophenyl* 4-*methyl*-4-p-*chlorobenzoyl-oxymethyl*-2-*oxazoline* (VIb). To compound Ib (2·2 g) dissolved in toluene (50 cc), *p*-chlorobenzoylchloride (1.7 g) was added and the mixture was refluxed for 2 hr. After removal of the solvent (red press), the residue was taken up in ether, the solution washed with 50% $K_2CO_3$ and dried over $K_2CO_3$. After removal of the solvent, the residue was dissolved in benzene–petrol ether 2:1 (30 cc), and chromatographed over alumina (30 g), each fraction (25 cc) being eluted with benzene–petrol ether 2:1. The first three fractions gave an oily residue; subsequent fractions gave 2 g of a crystalline product, which after crystallization from petrol ether yielded the pure ester (VIb), with m.p. 122–123°. (Found: C, 59·24; H, 4·31; N, 3·72; Cl, 19·28. $C_{18}H_{15}Cl_2NO_3$ requires: C, 59·35; H, 4·15; N, 3·85; Cl, 19·47%). Infra-red spectrum ($CHCl_3$): see Fig. 1.

*Reaction between* 2-(3′, 4′, 5′-*trimethoxyphenyl*)-4-*methyl*-4-*chlorocarbonyl-oxymethyl*-2-*oxazoline* (Ic) *and ammonia*. Chlorocarbonate Ic (1 g) was heated in a sealed tube for 24 hr at 80° with a saturated solution of anhydrous ammonia in dry dioxane (25 cc). After filtration and removal of the solvent (red press), the residue was treated with cold benzene, to give 0·5 g of crystals m.p. 178–179°. (Found: C, 56·66; H, 6·13; N, 6·67. $C_{19}H_{21}NO_5$ requires: C, 56·86; H, 6·20; N, 6·63%). This compound was identified as 3, 4, 5-trimetoxybenzamide by mixed m.p. and infra-red spectrum. The remaining benzene solution was evaporated to dryness (red press) and the oily residue (0·45 g), after treatment with absolute ether, gave crystalline material m.p. 65–75°. After repeated crystallizations from benzene–hexane, crystals of pure V m.p. 90–92° were obtained. (Found: C, 40·36; H, 5·29; N, 9·19; Cl, 23·85. $C_3H_5ClNO_2$ requires: C, 40·14; H, 5·39; N, 9·36; Cl, 23·70%). These crystals gave no m.p. depression with authentic V prepared as described. Their infra-red spectra were also identical.

The reaction between Ic and ammonia was also carried out at room temp according to the following procedure: a continuous stream of anhydrous ammonia was passed for 8 hr through a solution of Ic (0·439 g) in anhydrous chloroform (150 cc) then allowed to stand for several days, infra-red spectra being recorded from time to time. After the first 3 hr the infra-red spectrum was much the same as that of the starting material. Subsequent spectra, taken at intervals of about 8–10 hr, showed a progressive weakening of the band at 1795 $cm^{-1}$, together with the appearance of a new band of increasing intensity at 1764 $cm^{-1}$, and the persistance of a strong band in the region between 1684–1675 $cm^{-1}$.*

The reaction was discontinued only after a constant infra-red spectrum was obtained. Removal of

* The progressive disappearance of the chlorocarbonate derivative from the reaction mixture was responsible for the weakening of the 1795 $cm^{-1}$ band. The new band at 1764 $cm^{-1}$ was attributed to the carbonyl group present in the five-membered lactone ring of the cyclic urethane V, which was eventually isolated. The intense absorption between 1684–1675 $cm^{-1}$ in the initial spectra was attributed to the C=N stretching vibration of the oxazoline ring of the chlorocarbonate (Ic). However, since this product is gradually degraded by nucleophilic attack, the presence of such a band, even in the crude final product, must be due to the CO—NH absorption of the 3,4,5-trimethoxybenzamide; in fact, the latter shows in chloroform solution a strong absorption band at 1681 $cm^{-1}$.

the solvent and unreacted ammonia left a residue which, by treatment with a mixture of benzene–absolute ether 5:1, gave a solid material (0·25 g m.p. 172–174°). Crystallization from benzene yielded crystals m.p. 176–178°. (Found: C, 56·66; H, 6·13; N, 6·67. $C_{10}H_{13}NO_4$ requires: C, 56·86; H, 6·20; N, 6·63%). This substance was identified by mixed m.p. and infra-red spectrum as 3, 4, 5-trimethoxybenzamide. The remaining benzene–ether solution after removal of the solvents gave an oily residue which after long standing solidified completely. By repeated crystallizations from benzene–hexane, crystals of V were obtained m.p. 89–91°.

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# CALCULATION OF CONFORMATIONS OF ORGANIC MOLECULES*

A. I. KITAYGORODSKY
Institute of Organo-Element Compounds,
U.S.S.R. Academy of Sciences, Moscow

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**Abstract**—The most stable conformation of the molecule has a minimum of potential energy that arises due to the competition between the tendency of the valency angles to take ideal values and that of non-bonded atoms to be situated at an equilibrium distance. The equilibrium distance is equal to the sum of intermolecular radii determined by measuring the distances between atoms of adjacent molecules in the crystal. This idea is suggested as underlying a method of computation that enables to solve two problems. Firstly, the structure of the molecule being known, it becomes possible to ascertain the points of the interaction curve of the non-bonded atoms and secondly, with the interaction curve known, one can calculate the optimal configuration of the molecule.

To illustrate the suggested theory the conformation of molecules of some cyclic hydrocarbons has been calculated. It is to be stressed that the investigation of the conformation of strained molecules affords the main means of studying the interaction of non-bonded atoms.

## INTRODUCTION

THE theoretical calculation of geometrical parameters and the energy of conformation of molecules is of great interest. To this end it is necessary to possess information concerning some characteristic constants and functions that, in turn, can be derived by analyzing geometrical parameters and the energy of molecules whose structure has been determined.

This work aims at demonstrating the possibility of determining the interaction energy of non-bonded atoms by the molecular structural analysis. The empirical information thus obtained permits us the evalutation of the optimal conformation of molecules with unknown structure.

The following general considerations are underlying the suggested method of calculation. In the process of temperature vibrations the atoms of the molecule undergo complex movements without breaking the bonds. Thus there is a continuous series of conformations possible for a molecule. Various conformations differ in energy and therefore possess different probability.

The variation of conformation results, generally speaking, in the change of all its geometrical parameters such as the length of the bonds (or the equilibrium distances between the bonded atoms), the valence angles and the distances between the non-bonded atoms.

This investigation is based on the assumption of the addivity of the molecular energy, that is the overall energy can be separated into three additives responsible for the energy of the bonds, of the angles and of the non-bonded atoms. The issue is strongly facilitated by the fact that the chemical structure pre-determines the length of the bonds to as high a precision as 0·01–0·02 Å. The changes in conformation

* Translated by A. L. Pumpiansky, Moscow.

(e.g. the change of "boat → chair" cyclohexane conformation) does not lead to noticeable stretching of the bond length. This conclusion has been derived from structural investigations that show little difference in the bond length in highly strained structures and that of non-strained molecules (though bond stretching caused by the interaction of non-bonded angles up to 0·01 Å seems to be a real effect).

Thus, for example, the C—C bond lengths in cyclobutane and normal alkanes differ by about 0·02 Å.

There is no difficulty in showing that in the mechanical system of points linked by springs of different rigidity the deformation energies are in an inverse ratio to the forces constants. The rigidity of the bond is markedly higher than that of the angle or that of the interaction between the non-bonded atoms.

Any change of configuration is therefore connected with the change of both the valence angles and distances between the non-bonded atoms. Let the conformation strain energy be the sum of two additives

$$U = V + \Phi$$

where the energy $V$ is connected with the value of the valent angles and energy $\Phi$ with the distance between the non-bonded angles.

The optimum configuration is that with the minimum value. Therefore it is of importance to determine the geometrical parameters that lead to the minimum $U$ value.

*The energy of the angle*

An ideal valence angle can be said to be such an angle that could exist in the absence of interaction between non-bonded atoms (as well as, of course, in the absence of bonds imposed by the added atoms). With $sp^3$ bonds such an angle is known to be the tetrahedrical angle at 109° 28′, with pure $p$ bonds the angle at 90°, etc. The deviation of the angle from its ideal value leads to a decrease of the orbital over-lapping and corresponding energy increase. For the deviations $\alpha$ from the ideal value which we met in practice the angle energy can be written down within the precision of the constant additive as $\frac{1}{2}C\alpha^2$ with $C$ being the coefficient that can be, in principle, calculated by resorting to quantum chemistry.[1]

This not being practically the case we shall consider the coefficient $C$ as an empirical coefficient and, in addition, as a constant value for the atom that is in the apex of the angle and not depending on the type of the bonded atoms. We shall refer of coefficient $C$ as the ideal angle force constant. Its relation to the force constant of the angle $k_\beta$ deduced from the analysis of the molecular vibration will be discussed below.

The energy connected with the value of angles is $V = \Sigma\frac{1}{2}C\alpha^2$, the summation embracing all valence angles.

*The interaction between the non-bonded angles*

Investigating different problems due to steric interaction a number of authors attempted to formulate the interaction energy–distance ratio. The first attempt dealing with the interaction between hydrogen atoms seems to be due to Eyring[2]

[1] e.g. C. A. Coulson, *Valence*. Oxford (1953).
[2] H. Eyring, *J. Amer. Chem. Soc.* **54**, 3191 (1932).

who evaluated the repulsion energy as $Q_{HH} - \frac{1}{2}T_{HH}$, with $Q$ and $T$ being the Coulomb and exchange integrals and the attraction energy taken from the well known work by London as $A/r^6$. The recent calculations of this type are those by Hirschfelder and Linnett[3] that have been used by Mason and Kreevoy[4] as well as by Adrian.[5]

The calculations used in the works cited above cannot be regarded as correct as they lead to the minimum interaction energy lying at the value 4·5 Å. It is at the same time a well established fact that the equilibrium distance for two non-bonded hydrogen atoms is 2·35 Å. Within the limits of precision not less than 0·1 Å this distance is realized for hydrogen atoms in molecules possessing quite different properties. There is no reason to believe that this figure, deduced from the analysis of inter-molecular contacts in the crystal, may be substantially different for hydrogen atoms of the same molecule.* The constancy of intermolecular radii, their negligible dependance on the dipole moments and chemical properties[6] gives us a definite knowledge of an important point on the interaction curve of the non-bonded atoms, namely that of the co-ordinate of its minimum. The theoretical methods available do not result in the necessary value of the curve minimum, this being due to the imperfection of calculations.

The main thesis of our work is the assertion that: *the non-bonded atoms of the molecule at a distance greater than the sum of their intermolecular radii are only negligibly attracted to each other, those at a distance smaller than that sum being repelled from each other to a considerable extent.*

This fact, though not clearly formulated, is taken into account in the works of Dostrovsky *et al.*,[7] as well as Westheimer and Mayer[8] who chose their interaction curves so that their minimum would correspond to the sum of the intermolecular radii. This adjustment is effected by varying the coefficients in the formulae such as $(a/r^m) - (b/r^n)$ or $Ae^{-\alpha r} - (b/r^n)$.

In this work we decided not to make use of any analytical expressions. It must however be stressed that the interaction curve of the non-bonded atoms must not be calculated but found experimentally (see below). It is thereby neither necessary nor possible to take the physical factors, affecting the interaction, separately. The same considerations apply to the electro-static field that, by the way, is of little effect on the changes in energy owing to the electric potential being slow, as indicated in the work cited above.[4]

The interaction curve is steeply rising over the range of repulsion and extremely gently sloping over that of attraction (the minimum of the interaction curve, as judged by the heat of sublimation per the pair of interacting atoms, is as small as tens of parts of kcal/mole). Therefore, in most conformation problems attraction can be easily dispensed with, and the interaction energy of non-bonded atoms can

* There is no doubt about the dependence of the atom radius on the direction of the radius depending on the direction of the bond. This dependence is however not yet sufficiently investigated and therefore not taken into consideration though it could have been easily allowed for in the approach under study. One must also bear in mind the influence of the crystal field on the atom interaction curve. Therefore the equilibrium distances of non-bonded atoms can be said to be different, depending on the aggregate state.

[3] J. O. Hirschfelder and J. W. Linnett, *J. Chem. Phys.* **18**, 130 (1950).
[4] E. A. Mason and M. M. Kreevoy, *J. Amer. Chem. Soc.* **77**, 5808 (1955).
[5] F. J. Adrian, *J. Chem. Phys.* **28**, 608 (1958).
[6] A. I. Kitaygorodsky, *Organic Crystal Chemistry*. Moscow (1955), London Engl. transl. Infosearch (1960).
[7] I. Dostrovsky, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* 173 (1946).
[8] F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.* **14**, 733 (1946).

be accounted for as $\Phi = \Sigma f(\Delta r/r_0)$ extending the summation to all pairs of atoms at a distance less by $\Delta r$ than the equilibrium distance $r_0$. It is more convenient to write the interaction energy of a pair of atoms as the function of the relative decrease $\Delta r/r_0$ of the distance between them.

*The conditions for the optimum conformation*

The conformation of a molecule is characterised by a definite number of independent parameters $\varepsilon_i$, that can be expressed in terms of some valence angles, or the distances between the non-bonded atoms, or other geometrical parameters. When the molecule consists of $n$ atoms linked by $m$ bonds the number of parameters is $3n-6-m$. The symmetry of the molecule decreases the extent of freedom. To arrive at the optimum conformation it is necessary to differentiate the energy expression

$$U = \tfrac{1}{2}\Sigma C\alpha^2 + \Sigma f\left(\frac{\Delta r}{r_0}\right)$$

by all independent parameters $\varepsilon_i$,
Equations

$$\frac{\partial U}{\partial \varepsilon_i} = \Sigma C\alpha \frac{\partial \alpha}{\partial \varepsilon_i} + \Sigma f'\left(\frac{\Delta r}{r_0}\right)\frac{\partial(\Delta r)}{r_0\,\partial \varepsilon_i} = 0$$

allow to arrive at the value $f'/C$ for definite values of arguments provided the structural values of the molecule in question are available. On the other hand, the curve $f'/C$ being known, one can determine the optimum conformation of the molecule.[9] We shall refer to the value $\eta = f'/C$ as *the relative force of the interaction of atoms.*

*The shape of the relative force curve*

The constant $C$ must depend on the central atom whilst $\eta(\Delta r/r_0)$ characterizes the interaction of definite atoms. To solve our problem it is therefore necessary to acquire structural information about a rather great number of molecules of the same atoms but with different valence angles and spacing of the non-bonded atoms. Unfortunately at present this information is scarce.

To demonstrate the possibility of the suggested approach to the conformational problem we have, however, attempted to calculate a number of conformations. The curve $\eta$ that we have decided to make use of is shown in Fig. 1, the points obtained by calculating $\eta$ for simple molecules. It will be seen that the points referring to the interaction between carbon and hydrogen atoms bound to different atoms are situated on the same curve. It is of interest, that the energy interaction curve for carbon and bromine atoms, as reported by Dostrovsky *et al.*[7] and recalculated in terms of the values of the relative force $\eta$ is rather similar to our mean curve.

Whether this coincidence is occasional, how great are the changes of the curve $f'$ for different atoms and coefficients $C$ for central atoms can be shown only by further practical investigations of the molecular structure. It is however at present safe to say that the interaction curve for the halogen atoms is markedly steeper.

*Calculation of conformations*

In the table the conformational calculations for a number of hydrocarbons are given. It is quite possible that in the future the shape of the curve $\eta$ we have

[9] A. I. Kitaygorodsky, *Dokl. Akad. Nauk SSSR* **124**, 1267 (1959).

used will have to be substantially changed. This will, however, not seem to affect the general character of the calculated distortions.

From the data obtained it is above all to be noted that the tetrahedral angles in normal alkanes and cyclohexane are increasing up to about 111·5°; and that the HCH angle in cycloalkanes is steadily decreasing (Fig. 2).

In addition to these simple systems three bridge structures have been calculated, only for one of which experimental data were available (Fig. 3).

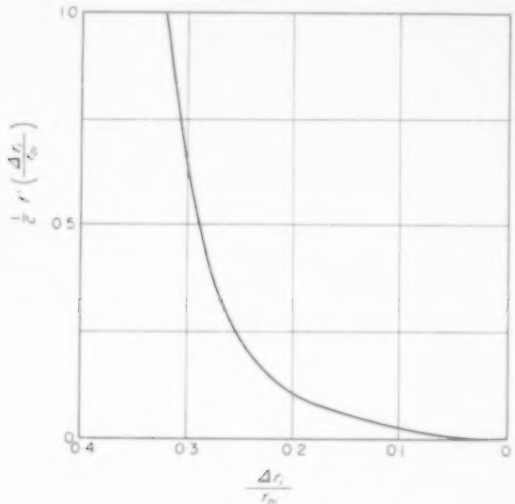


FIG. 1. Relative force of interaction of non-bonded atoms.

In Fig. 4 are listed data for acenaphtene, the calculation having been made for the values of the ideal angles (120°) and the tetrahedral value of the angle at atom 7. The calculations were compared with experimental data recorded by Ehrlich[10] (two mean values obtained from two independent measurements).

To exemplify the numerical calculation method let us take the simplest case of the conformation of the methylene group.

Let us denote ∠CCC as $\alpha$, ∠HCH as $\beta$, and ∠HCC as $\gamma$ with $\alpha$ and $\beta$ being independent parameters. If their value deviate by $\Delta\alpha$ and $\Delta\beta$ from the ideal value (109° 30′); then from the correlation $\cos\gamma = -\cos(\alpha/2) \cdot \cos(\beta/2)$ it follows with reasonable precision that $\Delta\gamma = -\frac{1}{4}(\Delta\alpha + \Delta\beta)$. The interatomic distances are represented by expanding trigonometrical functions about the ideal value of the angle.

Hence

$$r_{CC} = 2{\cdot}50 + 0{\cdot}88\Delta\alpha, \qquad r_{HH} = 1{\cdot}76 + 0{\cdot}62\Delta\beta$$

and

$$r_{CH} = 2{\cdot}15 - 0{\cdot}18(\Delta\alpha + \Delta\beta).$$

The relative contractions are found by applying intermolecular radii $R_C = 1{\cdot}8$ and $R_H = 1{\cdot}2$ Å.

[10] H. W. W. Ehrlich, *Acta Cryst.* **10**, 699 (1957).

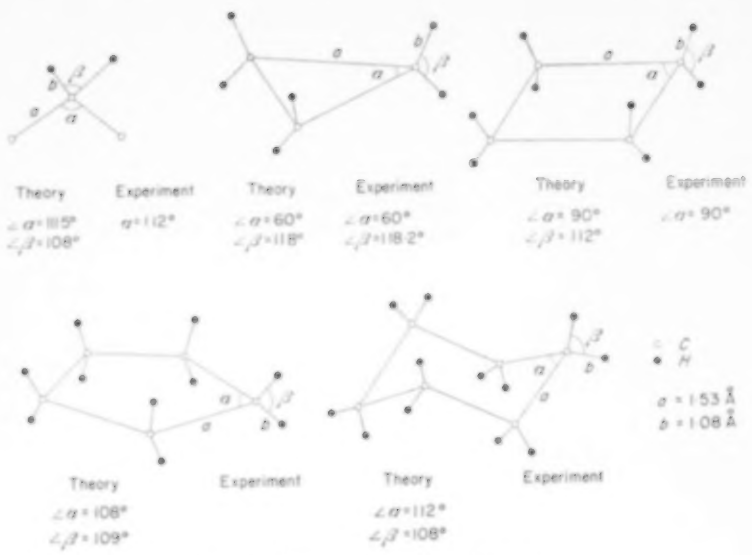


FIG. 2. Conformations of cycloalkanes.

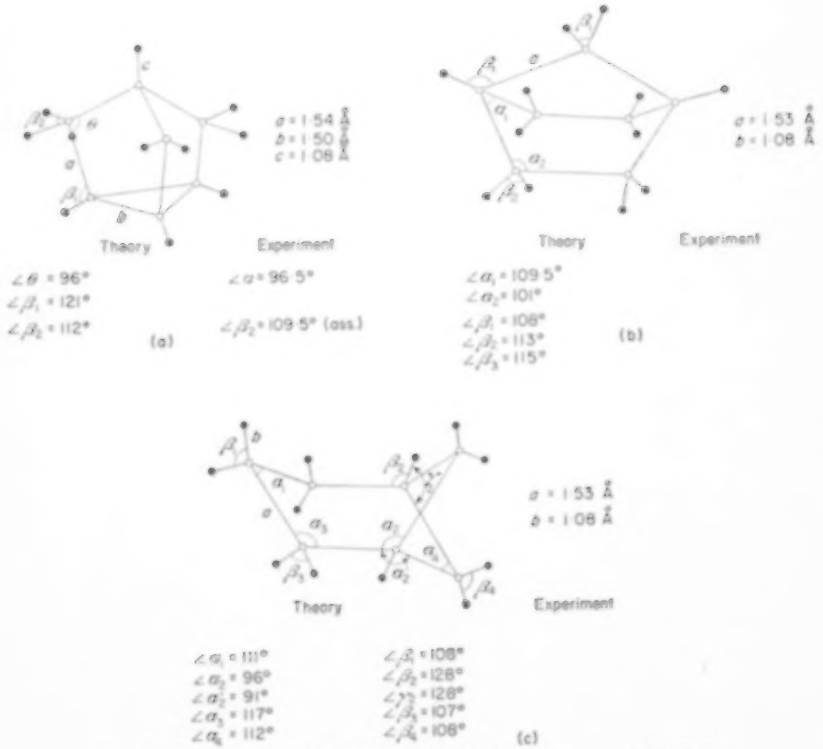


FIG. 3. Conformations of (a) nortricyclene $C_7H_{10}$, (b) norcamphane $C_7H_{12}$, (c) norpinane $C_7H_{12}$.

Thus, the expression for the strain energy of the methylene group can be represented as

$$U = \frac{C}{2}[(\Delta\alpha)^2 + (\Delta\beta)^2 + \tfrac{1}{4}(\Delta\alpha + \Delta\beta)^2] + f(0{\cdot}306 - 0{\cdot}245\Delta\alpha) + f(0{\cdot}267 - 0{\cdot}26\Delta\beta) + 4f(0{\cdot}283 + 0{\cdot}06(\Delta\alpha + \Delta\beta))$$

Differentiating by $\Delta\alpha$ and $\Delta\beta$, equating the value of derivatives to zero and expanding $\eta(\Delta r/r_0)$ into the Taylor's series neglecting the second and higher powers of increments

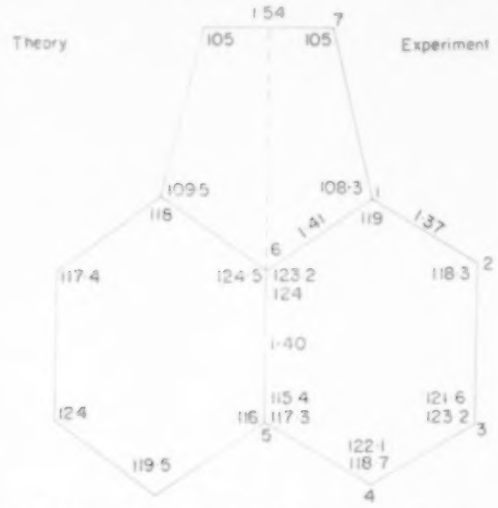


FIG. 4. Comparison of experiment and calculation for acenaphtene.

(values $\eta$ and $\eta'$ being taken from the above curve), one obtains two equations with two unknown quantities

$$\Delta\alpha + \tfrac{1}{4}(\Delta\alpha + \Delta\beta) - 0{\cdot}245(0{\cdot}75 - 5{\cdot}2\Delta\alpha) + 0{\cdot}24[0{\cdot}43 + 0{\cdot}64(\Delta\alpha + \Delta\beta)] = 0$$

$$\Delta\beta + \tfrac{1}{4}(\Delta\alpha + \Delta\beta) - 0{\cdot}26(0{\cdot}285 - 1{\cdot}3\Delta\beta) + 0{\cdot}24[0{\cdot}43 + 0{\cdot}64(\Delta\alpha + \Delta\beta)] = 0$$

whose solution leads to $\Delta\alpha = 0{\cdot}033$ and $\Delta\beta = -0{\cdot}025$. That is, the equilibrium values of the angles are 111·5° for ∠CCC and 108° for ∠HCH.

The same approach is applied to solve other cases, more complicated ones necessitating more than two equations.

*Deviations from coplanarity in aromatic systems*

At present there are well known instances of marked deviations from coplanarity in aromatic systems [e.g. see ref. (11)].

There is no need to exemplify this phenomenon by complex aromatic systems for non-planarity in aromatic nuclei appears to occur in all benzene derivatives. Indeed, the spacings of all substituents in the benzene ring are smaller than the sum of intermolecular radii. This results in repulsion that leads not only to the substituents being eliminated from the plane of the nucleus but also "dragging" carbon

[11] E. Harnik, F. H. Herbstein and G. Schmidt, *J. Chem. Soc.* 3288 (1954).

atoms with them and thereby making the benzene ring devoid of planarity. Conformational studies show that for the "triangular edge" of the benzene ring to be bent no great effort is required. Fig. 5 shows the conformation in the di-*p*-xylelene molecule. The above formulas were used to calculate the derivatives by independent parameters, in that case the deviations from the ideal angles $\Delta\alpha_1$, $\Delta\alpha_2$, and $\Delta\beta_1$. The fourth parameter was represented by angle $\varepsilon$, formed by the bent edge and the plane of the four central atoms. It was thereby noted that substituting experimental data in expressions for derivatives $\partial U/\partial(\Delta\alpha_1)$, $\partial U/\partial(\Delta\alpha_2)$ and $\partial U/\partial(\Delta\beta_1)$ converts them with reasonable precision to zero. At the same time $\partial U/\partial\varepsilon = 0{\cdot}3C$.

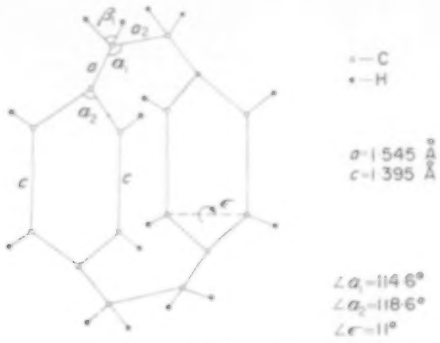


FIG. 5. Molecule of di-*p*-xylylene $C_{16}H_{16}$.

This points to the necessity of introducing into the energy member the energy due to the bending of the benzene ring. If this additive be substituted as $4(\gamma\varepsilon^2/2)$ and the experimental value of $\varepsilon$ is ~0·20 rad, then $\gamma = 0{\cdot}4C$. It will be thereby seen that the force constant of the edge bending is two and a half times less that of the ideal angle.

Of course the force constant of the edge bending cannot be regarded as established, being calculated only in one instance. It is moreover quite possible that such a strain energy characteristic of a distorted aromatic system is not strictly valid. We have, however, made use of these approximate data to estimate the distortions in such a structure as that of hexamethylbenzene. The strain energy expression is as follows

$$U = 6\frac{C}{2}[(\Delta\alpha)^2 + 2(\Delta\beta)^2] + 6f_{C_2C_3} + 12f_{Me_1C_2} + 6f_{Me_1Me_2} + \\ + 3f_{C_1C_3} + 3\frac{0{\cdot}4}{2}C(\Delta x)^2$$

with $\alpha = \angle CCC$, $\beta = MeCC$, and $\Delta x$ being the bending angle of the benzene ring edge. The molecule is believed to have a boat conformation. The drawing apart of two methyl groups proceeds at the expense of the bending of the edge bending and, in addition, at the expense of the expulsion of the methyl group from the plane of the respective carbon atom triangle, the latter deviation being due to that of the angle $\beta$ from 120°.

The minimum potential energy proved to be at the angle value $\Delta x = 8°$. The adjacent methyl groups are drawn thereby further apart at the expense of the deviation

of the C—$CH_3$ bond by the angle 6° from the plane of the respective benzene nucleus triangle.

Such example of a similar, highly distorted system can be provided by the structure of a benzene derivative determined by Struchkov[12] at our Institute (see Fig. 6). The

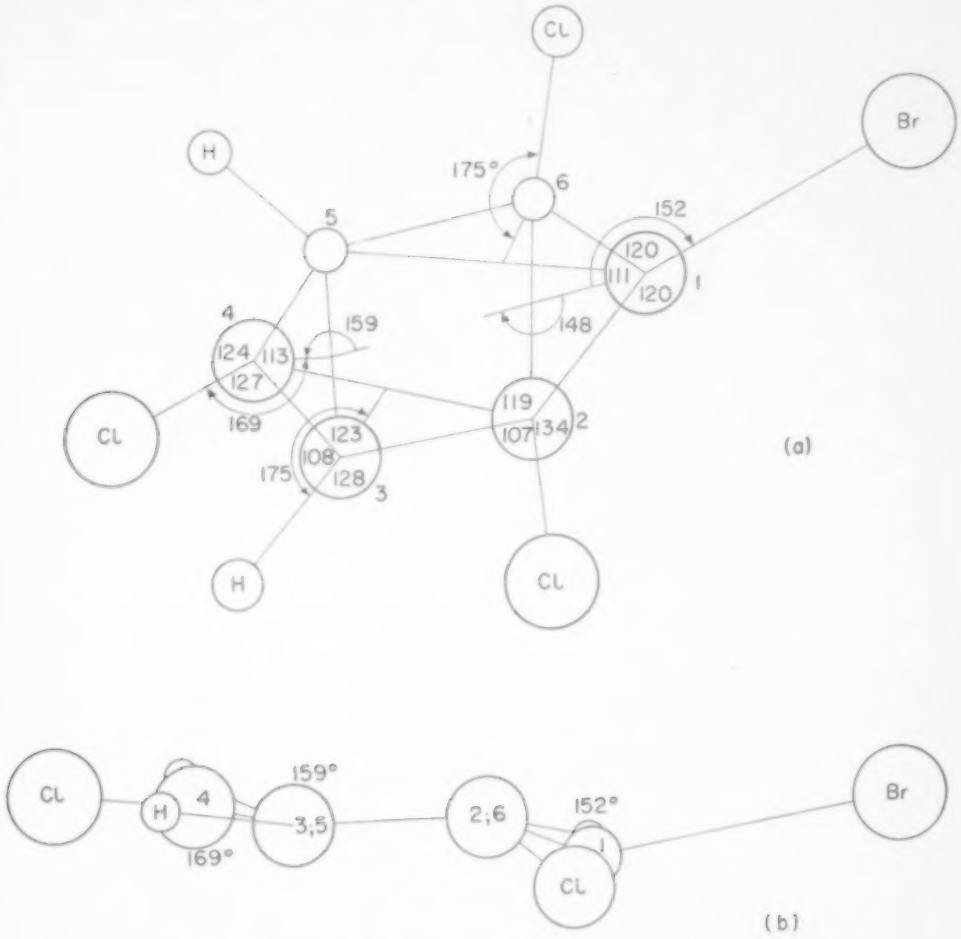


FIG. 6. Experimental data of molecule of 1-bromo-2,4,6-trichlorobenzene:
(a) perspective view,
(b) view in the direction perpendicular to the symmetry plane.

distortion of the ring is very strong, the benzene ring conformation being near to that of the boat conformation in cyclohexane.

The evaluation of the coefficient $C$ (see below) allowed us to compute the difference in the energy of optimal and flat configurations. It proved to be less than 0·1 kc/m. Thus the influence of the crystal field can lead to the molecule becoming flat. In other instances, however, the crystal molecules can also deviate from the flat form.

[12] J. T. Struchkov and S. L. Solenova, *Proc. Moscow State Univ.* **12**, 1228 (1959).

*Evaluation of strain energy and rigidity coefficients*

Conformational analysis leads us to the estimation of the relative interaction force $\eta = f'(\Delta r/r_0)/C$ value. The estimation of the absolute force value and the calculation of the interaction energy is therefore possible only by taking into account other physical considerations as well.

Coefficient $C$ can be, as already mentioned above, calculated in terms of quantum chemistry. These calculations being extremely rough, it seems of greater importance to determine $C$ from the optical force constant $k_\beta = \frac{1}{N}\left[\frac{\partial^2 U}{\partial \beta^2}\right]_{\beta=\beta_0}$ where $\beta_0$ is the equilibrium value and $N$ the number of equivalent angles.

Having established $k_\beta$ and the relative force $\eta$ curve we can determine the constant $C$. This correlation allows us also to check the degree of precision of our assumption on the coefficient $C$ being dependent only upon the central atom properties. Indeed, if the apexes of the $\beta$ and $\gamma$ angles are in the same atom, then $k_\beta$ and $k_\gamma$ can be expressed by the same ideal angle force constant $C$.

Denoting the HCH and HCC angles in cyclopropane through $\beta$ and $\gamma$, respectively and bearing in mind that the deviations $\Delta\beta$ and $\Delta\gamma$ of these angles from the tetrahedral values are related by the correlation

$$\Delta\gamma = 0{\cdot}175 - 0{\cdot}374\Delta\beta$$

one obtains

$$k_\gamma = \frac{1}{12}\frac{\partial^2 U}{\partial \gamma^2} \quad \text{and} \quad k_\beta = \frac{1}{3}\frac{\partial^2 U}{\partial \beta^2}$$

As $\dfrac{\partial^2 U}{\partial \beta^2} = \dfrac{\partial^2 U}{\partial \gamma^2}\left(\dfrac{\partial \gamma}{\partial \beta}\right)^2 = 0{\cdot}15\,\dfrac{\partial^2 U}{\partial \gamma^2}$, then $\dfrac{k_\gamma}{k_\beta} = 1{\cdot}7$,

in agreement with the experiment

$$\left(k_\gamma = 0{\cdot}5 - 0{\cdot}6\,\frac{\text{erg}}{\text{rad}^2}, \quad \text{and} \quad k_\beta = 0{\cdot}30 - 0{\cdot}35\,\frac{\text{erg}}{\text{rad}^2}\right).$$

The potential energy expression for cyclopropane is as follows

$$\tfrac{1}{3}U = \frac{C}{2}\,/(\Delta\beta)^2 + 4(0{\cdot}175 - 0{\cdot}374\Delta\beta)^2/ + f(0{\cdot}267 - 0{\cdot}26\Delta\beta) + 4f(0{\cdot}243 + 0{\cdot}086\Delta\beta)$$

Twice differentiating and dividing both sides of equality by $C$ one obtains $k_\beta/C = 2{\cdot}0$.

Thus, the approximate value of the ideal angle constant of the tetravalent carbon atom can be taken as equal $C = 0{\cdot}1_7.10^{-11}$ erg/rad$^2$.

Having ascertained $C$ one finds $f'(\Delta r/r_0) = C\eta(\Delta r/r_0)$ and through graphical integration determines the repulsion energy of non-bonded hydrogen and carbon atoms. Our averaged curve $\Lambda$ is rather similar to the interaction curve of carbon and bromine atoms reported by Dostrovsky *et al.*[7] but markedly different from those of Mason and Kreevoy. The latter interaction curves have been construed without allowing for the intermolecular radii and represent repulsion of even those atoms (in a molecule) that are not immediately adjacent to each other.

The interaction potential of non-bonded atoms seems to drop much faster and,

within a fair approximation, the conformation in the molecule and the strain energy appear to be determined only by the interaction of adjacent neighbouring atoms that are in immediate contact with each other.

It is to be recalled that the aim of the present paper is primarily to suggest a definite method to deal with the problem in question. As to the quantative approach it is thought to be subject to changes.

At present very little is known about the structure of strained molecules and the distortion of valence angles caused by the interaction of non-bonded atoms. The accumulation of experimental evidence will enable to determine more exactly the interaction curves for various pairs of atoms and to calculate *a priori* the optimum conformation in any molecule of a known chemical structure.

The author wishes to express his gratitude to Mrs. K. Myrskaya for computational assistance.

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# RESEARCHES ON THE AROMATIC AZO COMPOUNDS

## THE OXIDATION OF *p*-DIMETHYLAMINO-PHENYLAZO-PYRIDINES

L. PENTIMALLI
Istituto di Chimica degli Intermedi, Facoltà Chimica Industriale, Bologna

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**Abstract**—This paper concerns the mono-oxidation of the three isomeric *p*-dimethylamino-phenylazo-pyridines by perbenzoic acid. The 2-isomer leads only to the amino-oxide; the 3-isomer yields mainly the amino-oxide, and small amounts of the 1-oxide. With the 4-isomer a mixture was obtained, from which only the 1-oxide was isolated. These results are discussed on the basis of the absorption spectra and resonance structures of the azo compounds.

THE results of the mono-oxidation of 2-(*p*-dimethylamino)-phenylazo-pyridine have previously been reported.[1] The oxidation of the dimethylamino group and not the pyridine nitrogen as might be expected on the basis of the acidity constants, suggests a revision of the concepts of resonance in the arylazo-pyridine system. It must be assumed that the conjugation of the dimethylamino group and the pyridine ring does not occur sufficiently to give the pyridine nitrogen an electron density greater than the initial value on the amino nitrogen. In order to discuss the reasons for this the behaviour of the other position isomers was investigated by mono-oxidation with organic peracids. This is a convenient method for evaluating the relative electron density on the different nitrogen atoms of the molecule. The experimental results of the mono-oxidation of 2-(*p*-dimethylamino)-phenylazo-pyridine (I) show that the

I II

first oxygen atom goes to the dimethylamino group, which suggests a similar course for the 3-isomer (III). The basicity of the amino nitrogen in the 2-isomer due to the lack of conjugation by electromeric effect via the azo group to the pyridine nitrogen,

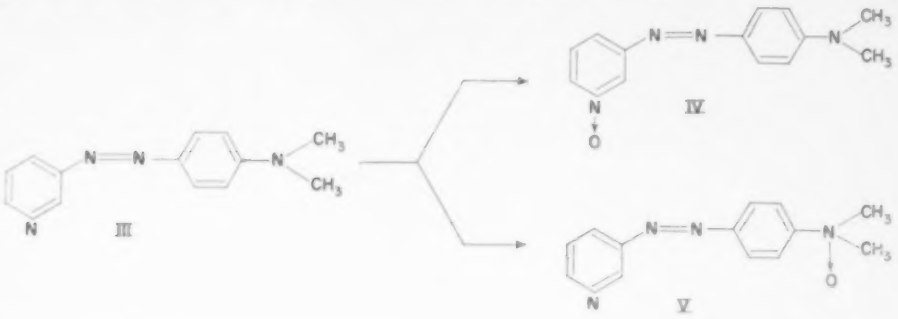
III

must occur in the 3-isomer where such conjugation is impossible. The pyridine nitrogen in *meta* position is not inhibited by the —M-effect of the azo group and the electron density on it can be greater than in the 2-isomer.

Mono-oxidation of III gave a mixture from which the principal product, an orange

[1] L. Pentimalli, *Gazz. Chim. Ital.* **89**, 1843 (1959).

coloured compound, was isolated, corresponding to the mono-oxidized azo compound with a spectrum almost identical to that of 3-phenylazo-pyridine (Figs. 1 and 2).



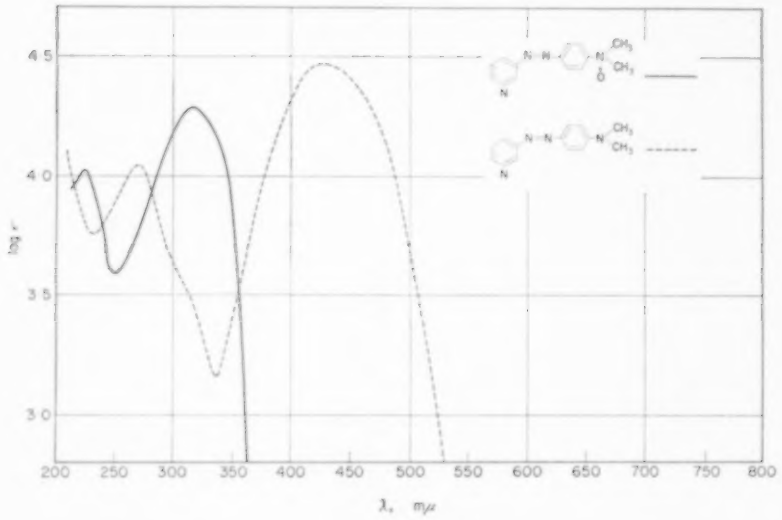



FIG. 1.

Besides the amino-oxide V it was possible to isolate a small amount of the 1-oxide IV (Fig. 3), identified by direct comparison with a sample obtained by synthesis.[2] Table 1 summarizes the spectrophotometrical data.

The first oxygen atom therefore goes preferentially to the amino nitrogen. The small amount of the 1-oxide indicates that the pyridine nitrogen in the 3-isomer has an electron density greater than in the 2-isomer.

Oxidation of this kind of molecule by organic peracids presents difficulties, especially concerning the constancy of the results. This is caused by the easy cleavage of the azo molecule since the mono-oxidation often led to low yield even when no unchanged starting material was recovered.

Comparison of spectrophotometrical data of the *p*-dimethylamino-derivatives may be useful for understanding the relative behaviour of the different isomers (Fig. 4). The characteristic data are collected in Table 2.

[2] R. W. Faessinger, P. L. Malloy and E. V. Brown, unpublished work; private communication by E. V. Brown.

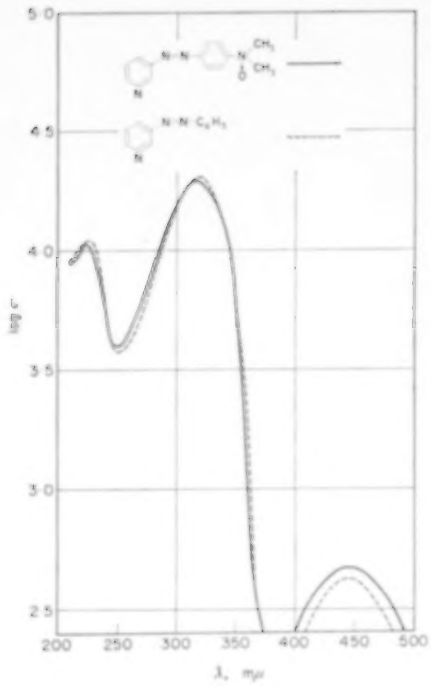



FIG. 2.

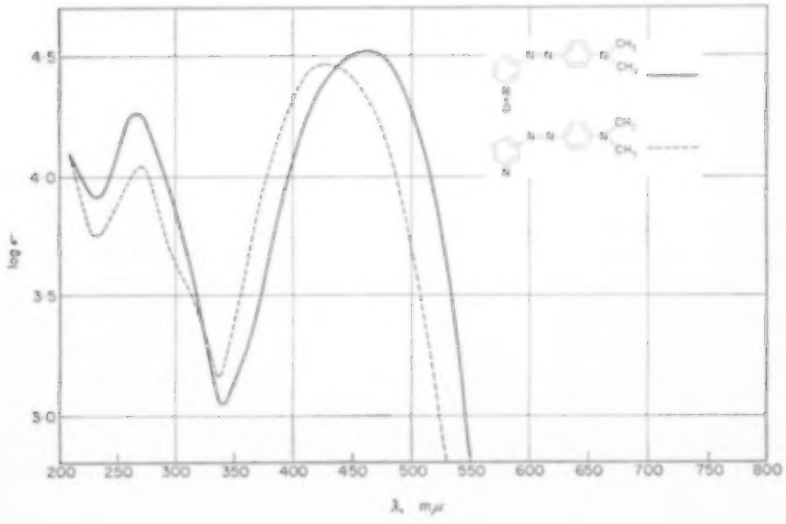



FIG. 3.

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TABLE 1. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (LOG ε) IN THE ABSORPTION SPECTRA OF 3-(*p*-DIMETHYLAMINO)-PHENYLAZO-PYRIDINE AND RELATED N-OXIDES IN ETHANOL

| | | $\lambda_1$ | $\lambda_2$* | $\lambda_3$ | $\lambda_4$ |
|---|---|---|---|---|---|
| 3-isomer | III | 272(4·03) | | 428(4·46) | |
| 3-isomer 1-oxide | IV | | 268(4·26) | 464(4·51) | |
| 3-isomer amino-oxide | V | 224(4·02) | | 316(4·29) | 444(2·67) |
| 3-phenylazo-pyridine | | 224(4·04) | | 318(4·30) | 444(2·63) |

* $\lambda_2$ indicates the $\lambda_{max}$ of the pyridine-1-oxide band.

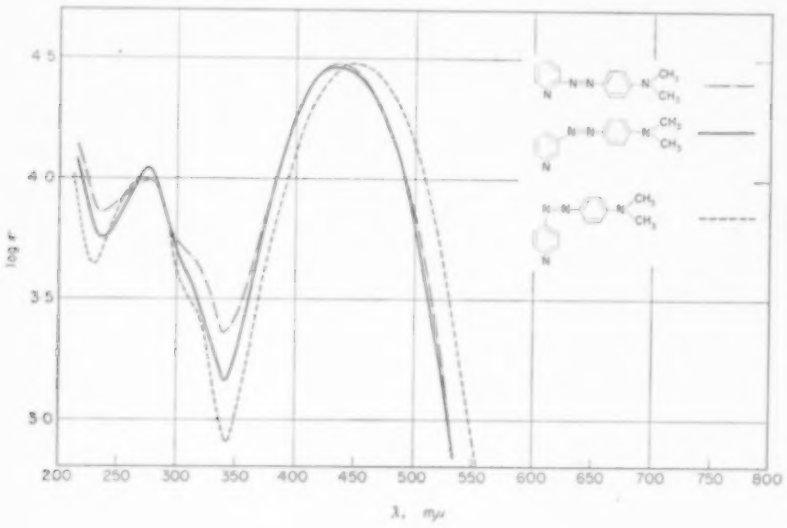


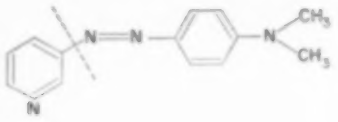

FIG. 4.

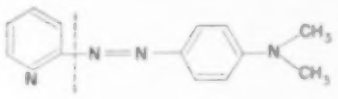
TABLE 2. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (LOG ε) IN THE ABSORPTION SPECTRA OF ISOMERIC *p*-DIMETHYLAMINO-PHENYLAZO-PYRIDINES IN ETHANOL

| | $\lambda_1$ | $\lambda_2$ |
|---|---|---|
| 2-(*p*-dimethylamino)-phenylazo-pyridine | 273(3·99) | 432(4·47) |
| 3-(*p*-dimethylamino)-phenylazo-pyridine | 272(4·03) | 428(4·46) |
| 4-(*p*-dimethylamino)-phenylazo-pyridine | 272(4·00) | 444(4·48) |

Although the curves show no marked differences, it may be observed that the curves of the 2- and 3-isomers are almost identical. The 2-isomer shows a short 4 mμ shift in comparison with the 3-isomer, while the 4-isomer shows a significant red shift of about 12 mμ in comparison with the other two. However, it is apparent that neither of the two conjugate azo compounds (2- and 4-isomers) shows major

shifts with regard to the non-conjugate azo compound (3-isomer). The conjugation K band ($\lambda_3$) may therefore be related to the principal conjugation of the molecule, certainly due to the dimethylamino group but involving to a negligible extent the pyridine ring.




As in the case of the phenylazo-pyridines, the molecules must be represented with the main chromophoric system including only the azo group, since interaction between the azo group and the pyridine ring should involve substantial differences of the absorption depending on whether or not the phenylazo substituent is in a conjugate position.

Examination of absorption spectra in acidic media to observe the protonation electronic effect on the nitrogen atoms, as with the unsubstituted phenylazo-pyridines,[3] was not suitable because protonation leads to a tautomeric equilibrium[4] and serves only to complicate certain aspects of the problem.

The spectroscopic measurements in neutral medium (ethanol) show therefore for the three isomers, at the ground state in inactive media, a conjugate phenylazo structure with no significant effect of the pyridyl group: the *ortho-meta* equivalence is striking in this respect (Fig. 4); hence, in the arylazo-pyridines, in inactive media, the azo group (electron-acceptor) behaves as an insulator between the two electronic oscillators. The 2- and 4-isomers of the arylazo-pyridines, in the normal state, may therefore properly be regarded as potentially conjugate rather than conjugate azo compounds, an electromeric effect remaining where the possible mesomeric effect fails to occur.

The presence of the dimethylamino group in *para* position, affecting the azo group to a greater extent, opposes the electron pull of the azo group on the pyridyl, and the basicity of the pyridine nitrogen is increased to about the same extent for the 2- and 4-isomers.

TABLE 3. ACIDITY CONSTANTS, pKa, AT 25°

| | Pyridinium | Azonium | Ammonium |
|---|---|---|---|
| 2-phenylazo-pyridine[3] | 2·0 | −3·1 | — |
| 4-phenylazo-pyridine[3] | 3·5 | −3·1 | — |
| 2-(*p*-dimethylamino)-phenylazo-py[4] | 4·5 | ... | 2·0 |
| 4-(*p*-dimethylamino)-phenylazo-py[4] | 5·8 | ... | 3·4 |
| pyridine | 5·3 | — | — |
| azobenzene[4] | — | −2·5 | — |

[3] L. Pentimalli, unpublished work; see M. Colonna and A. Risaliti, *Gazz. Chim. Ital.* **85**, 1148 (1955).
[4] I. M. Klotz, H. A. Fiess, J. Y. Chen Ho and M. Mellody, *J. Amer. Chem. Soc.* **76**, 5136 (1954); G. Cilento, A. Foffani and M. R. Foffani, *Rend. Accad. Lincei* [8] **23**, 60 (1957).
[5] E. C. Miller and J. A. Miller, *Ibid.* **78** 1718 (1956).

Comparison of the absorption curves of the *p*-dimethylamino-phenyl-azo-pyridines shows no appreciable conjugation for the 2-isomer, potentially conjugate, and the first oxygen atom adds exclusively to the amino nitrogen (in contrast to the assignments of the acidity constant values). The 4-isomer, on the other hand, shows an appreciable shift (+16 m$\mu$) with respect to the 3-isomer, which may be related to a more pronounced conjugation regarding the other members of the series. This agrees with the general case of 4-pyridine-derivatives, which always show a stronger conjugative effect than 2-derivatives.[6]

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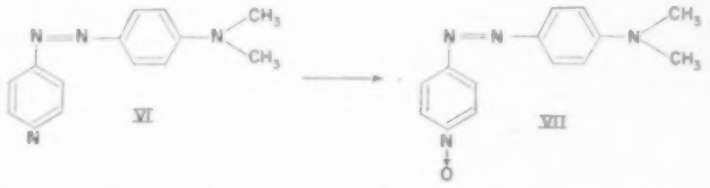
Also on the basis of the acidity constant (Table 3), markedly higher for the 4-isomer than for the 2-derivative, it may be anticipated that mono-oxidation will lead in this case to at least a mixture of oxidation products and the pyridine nitrogen atom can compete, to a greater or a lesser extent, with the amino nitrogen in accepting the first oxygen atom.

The experimental results gave a mixture from which (assuming the presence of the amino oxide) only the 1-oxide is isolated, from the pyridine nitrogen, which is not formed in the oxidation of the 2-isomer.




Identification of the oxidation compound was by direct comparison with the 1-oxide (VII) obtained by synthesis[2] and the absorption curves appeared to be identical (Fig. 5).

Attempts for further oxidation failed.

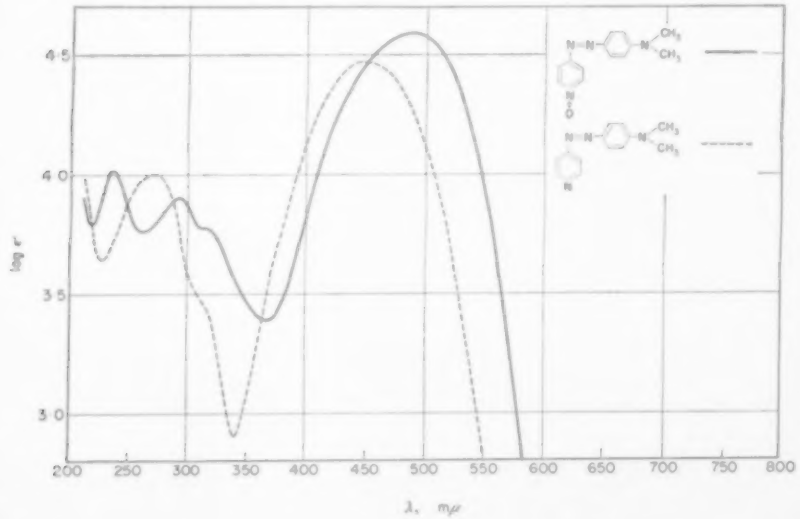



FIG. 5.

[6] see M. Colonna, A. Risaliti and L. Pentimalli, *Gazz. Chim. Ital.* **86**, 1067 (1956).

As a result of these investigations, it may be assumed that in the arylazo-pyridines the azo group appears to be an ineffective conjugation conductor, owing to its strong electron-acceptor character. With the 3-isomer, the first oxygen atom goes preferentially to the amino group, and only to a small extent to the pyridine nitrogen. The

TABLE 4. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (LOG ε) IN THE ABSORPTION SPECTRA OF 4-(*p*-DIMETHYLAMINO)-PHENYLAZO-PYRIDINE AND RELATED 1-OXIDE IN ETHANOL

| | | | |
|---|---|---|---|
| 4-(*p*-dimethylamino)-phenylazo-py (VI) | 272(4·00) | 292(3·90) | 444(4·48) |
| 4-*p*-dimethylamino-phenylazo 1-oxide (VII) | 236(4·02) | 292(3·90) | 490(4·59) |

2-isomer, in which the azo group may decrease the electron density on the pyridine nitrogen, yields only the amino oxide. With the 4-isomer, in which resonance is more pronounced as is the case for the pyridine 4-derivatives, a mixture was obtained from which only the 1-oxide was isolated in appreciable amounts.

## EXPERIMENTAL

3-(p-*Dimethylamino*)-*phenylazo-pyridine* (III). 3-Amino-pyridine (4·6 g) was diazotized and coupled with dimethylaniline. The mixture, after 1 hr at 0°, was neutralized with sodium carbonate; the separated azo compound was filtered, washed with iced water and dried. Yield 4·8 g. Red fine needles (benzene or ligroin), m.p. 123° (reported[7] 121°).

3-*Amino-pyridine*-1-*oxide, hydrochloride*. To a solution of 3-amino-pyridine (20 g, 0·20 mole) in pyridine (60 ml), at 0°, benzoyl chloride (36 g, 0·26 mole) was slowly added, with stirring. After 2 hr, the suspension was poured into cold water (500 ml) and the white precipitate filtered, well washed with water and dried. Yield 37 g of 3-(N-benzoyl)-amino-pyridine, white prisms (benzene-ligroin), m.p. 118° (reported[7] 119°). This derivative (40 g) was oxidized by hydrogen peroxide and acetic acid. Yield 30 g of 3-(N-benzoyl)-amino-pyridine-1-oxide, white prisms (ethanol) m.p. 209–210°.[2] The oxide, on hydrolysis with aqueous sodium hydroxide and the resulting solution acidified with HCl, gave 3-amino-pyridine-1-oxide hydrochloride (8 g), white needles (ethanol–ether), m.p. 291–292°.[2]

3-(p-*Dimethylamino*)-*phenylazo-pyridine*-1-*oxide* (IV). This was obtained from the hydrochloride and dimethylaniline.[2] Purple needles (benzene), m.p. 186°.

*Mono-oxidation of* III. To a solution of III (2 g, 1 mole) in chloroform (150 ml), at 0°, a solution of perbenzoic acid (1·5 moles) in chloroform was slowly added. After remaining overnight the per-acid had disappeared, and the mixture was shaken with saturated sodium carbonate solution, and dried (anhydrous sodium carbonate) filtered and the chloroform evaporated. The residue was washed with benzene and dissolved in hot acetone. On cooling, hemispherical clusters of 3-(*p*-dimethylamino-N-oxide)-phenylazo-pyridine (1 g), orange needles (acetone) m. p. 118–119°, were obtained (Found: N, 23·27; Calc. for $C_{13}H_{14}N_4O$: N, 23·12%). The benzene solution was poured on an alumina column. The lower orange band gave unchanged azo compound; often an upper purple band was obtained, which gave 0·2 g of purple needles (benzene), m.p. 183–186°, identical with 3-(*p*-dimethylamino)-phenylazo-pyridine-1-oxide.

3-*Phenylazo-pyridine*. Prepared by condensation of 3-amino-pyridine and nitrosobenzene in 50% KOH, according to Campbell *et al.*[8] Orange needles (petroleum ether), m.p. 50–51°.

4-(p-*Dimethylamino*)-*phenylazo-pyridine* (VI). Prepared by coupling diazotized 4-amino-pyridine with dimethylaniline.[2] Brick red needles (benzene–ligroin), m.p. 208°.

4-*Amino-pyridine*-1-*oxide, hydrochloride*. To a solution of 4-amino-pyridine (10 g, 1 mole) in pyridine (80 ml), at 0°, benzoyl chloride (18 g, 0·13 mole) was slowly added, with stirring. After 2 hr, the precipitate was collected, washed with ether and dried. Yield 14 g 4-(N-benzoyl)-amino-pyridine

[7] A. Binz and C. Räth, *Liebigs Ann.* **486**, 95 (1931).
[8] N. Campbell, A. W. Henderson and D. Taylor, *J. Chem. Soc.* 1281 (1953).

hydrochloride, m.p. 250°. The hydrochloride was dissolved in hot water (300 ml), filtered, and the filtrate neutralized with $NaHCO_3$. Yield 10·2 g of 4-(N-benzoyl)-amino-pyridine, white prisms (water) m.p. 202°.[9]

4-(N-benzoyl)-amino-pyridine (10 g) was oxidized by hydrogen peroxide and acetic acid, as with the 3-derivative. 4-(N-benzoyl)-amino-pyridine-1-oxide, white needles (water) m.p. 247–250°. The crude oxide was used for the next step.

4-(N-benzoyl)-amino-pyridine-1-oxide, hydrolysed with aqueous sodium hydroxide and the resulting solution acidified with HCl, gave 4-amino-pyridine-1-oxide hydrochloride, white needles (ethanol–ether) m.p. 181°.

4-(p-*Dimethylamino*)-*phenylazo-pyridine*-1-*oxide* (VII). From 4-amino-pyridine-1-oxide hydrochloride and dimethylaniline.[2] Long purple needles (ethanol), m.p. 212°.

*Mono-oxidation of* VI. This was oxidized with perbenzoic acid, as described for the 3-isomer. The residue was dissolved in benzene and the solution poured on an alumina column. The lower orange band gave little unchanged azo compound; from the upper purple band needles (ethanol or benzene), m.p. 211°, identical with 4-(*p*-dimethylamino)-phenylazo-pyridine-1-oxide, were obtained.

*Ultra-violet-visible absorption spectra.* The absorption spectra were determined in 95% ethanol with a Beckman Model DU Quartz spectrophotometer.

*Acknowledgement*—The author is indebted to Prof. Ellis V. Brown, Seton Hall University, South Orange, N.J., U.S.A., having kindly provided experimental details of his unpublished work.

[9] E. Koenigs, G. Kinne and W. Weiss, *Ber. Dtsch. Chem. Ges.* **57**, 1172 (1924).

Tetrahedron, 1960, Vol. 9, pp. 202 to 209. Pergamon Press Ltd. Printed in Northern Ireland

# ASYMMETRIC ANNELLATION EFFECTS—IV*

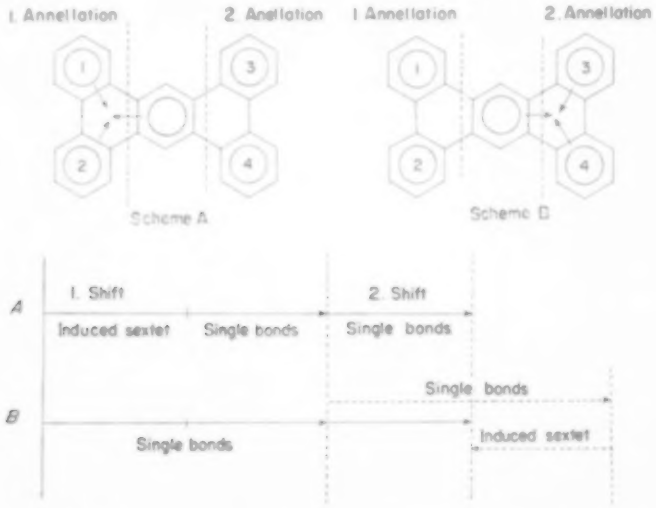
## DIBENZACENES

E. CLAR
Chemistry Department, The University of Glasgow

(*Received* 2 *December* 1959)

**Abstract**—The asymmetric annellation effects and the shift difference rule are explained on the basis of the two schemes A and B. The asymmetry of the annellation effects in passing from acenes to 1:2-benz-, and 1:2,3:4-dibenzacenes support the scheme B involving the view that the transition of a cyclic conjugated polyene into a benzenoid ring produces a violet spectral shift. Another set of asymmetric annellations is found in the heteronuclear dibenzacenes. This series can be started from ethylene. The merits of a symplified valence bond theory are considered for the interpretation of asymmetric annellation effects. The assumption of two transferable electrons capable of migrating through the rings of an acene leads to two $\pi$-electron levels for benzene with 4 $\pi$-electrons in two mobile double bonds in the lower level and 2 $\pi$-electrons moving freely about the ring and not belonging to any double bond.

ASYMMETRIC annellation effects are produced by two formally symmetrical substitutions of the benzene rings (1,2,3,4) to an acene system. These effects are observed as two very different red shifts of the $\beta$-bands. The nature of this electronic asymmetry becomes obvious if the second shift is subtracted from the first shift. This results in the



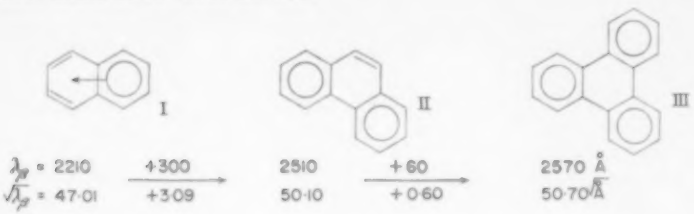

extension of the initial acene system to the next higher acene, i.e. from benzene to naphthalene, from naphthalene to anthracene, from anthracene to tetracene and from tetracene to the pentacene system etc.[1]

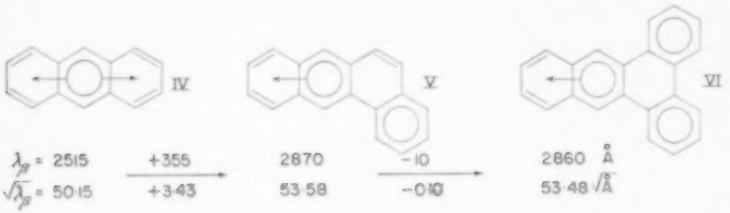
There are two interpretations of this empirical rule possible. The first interpretation (A) was given recently and keeps in line with conventional ideas about

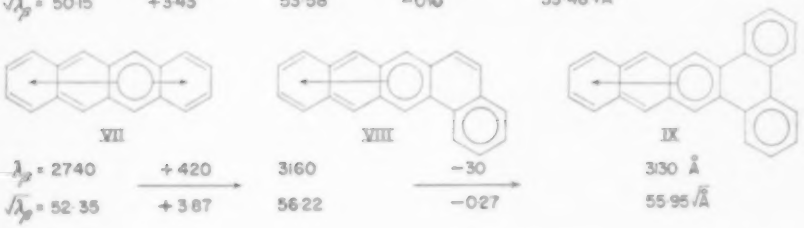
* Part III: *Tetrahedron* **6**, 358 (1959).

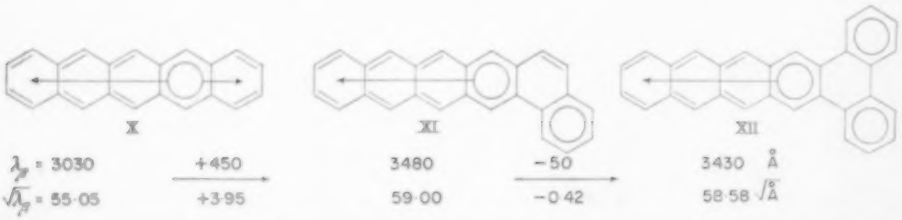
[1] E. Clar, *Tetrahedron* **6**, 355 (1959).

spectral conjugation and spectral shifts. Here the first shift consists of the sum of the shifts due to two single bonds, providing conjugation of the aliphatic type and to the shift resulting from the formation of an induced aromatic sextet, as indicated by the arrows. The deduction of the second shift gives the pure aromatic shift which thus must be towards the red.




In the second interpretation (B) the first shift is attributed to the single bonds alone, whilst the second one is considered to be the difference of the same shift *minus* the aromatic shift which must then be towards the short wave end of the spectrum. This means that a benzene molecule represented by one fixed Kekulé structure should absorb light at a longer wavelength than benzene with 6 mobile $\pi$-electrons, in an aromatic sextet.* The rule that the difference between the two shifts gives an increase amounting to one aromatic ring is valid in both interpretations (A and B).

A decision in favour of the scheme (B) can be reached if the annellation series I–XII is considered. The shifts are recorded in Å and $\sqrt{Å}$, the latter being a scale for the reciprocal nuclear charges. The first shifts (300, 355, 420 and 450) in these

* The aromatic sextet was first introduced by T. W. Armit and R. Robinson, *J. Chem. Soc.* 1604 (1925). In this paper its use is directly derived from it not involving the latter subdivision given to it.

four asymmetric annellation series are much bigger than the second ones (+60, −10, −30 and −50). If the principle of the maximum number of aromatic sextets is applied, then the acenes (I, IV, VII, X) can have only one benzenoid ring. The two transferable electrons can move through the system as indicated by the arrows. The fusion of the angular ring in (II, V, VII and XI) restricts this movement to one ring less, and this is the ring at the angle in which a double bond becomes fixed. This ring must therefore lose its acene character and thus produce a red shift. The fusion of the new ring with the third sextet has apparently very little influence, since the connection of the butadiene system in this ring brings about the same amount of red-shift just as the formation of the third sextet causes a violet-shift.

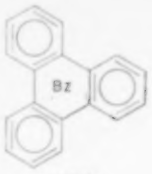
That this is the case is shown by the second annellation stage leading to (III, VI, IX and XII). Since the double bonds in the positions 3 and 4 are already fixed by the first annellation, the new rings fused to these positions must produce about the same amounts of red and violet shifts, thus resulting in a very small overall shift in comparison with the shift caused by the first annellation. Very small positive or negative annellation effects therefore are an indication of fixed double bonds at the position where a new ring has been fused. This can also be shown in the pyrene and perylene systems XIII and XV, where the application of the maximum number of benzenoid rings (marked with circles) enforces the fixation of double bonds. The annellation effects in passing to XIV and XVI are small violet-shifts (−30 and −55 Å respectively).

| | | | | | | |
|---|---|---|---|---|---|---|
| $\lambda_\beta$ = 2890 | −30 | 2860 | 3095 | −55 | 3040 | Å |
| $\sqrt{\lambda_\beta}$ = 53·76 | −028 | 53·48 | 5564 | −050 | 5514 | $\sqrt{Å}$ |

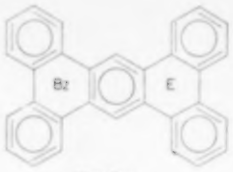
If the asymmetric annellation scheme (B) is accepted it is still not clear why an induced benzenoid ring is not formed in the first stage of the annellation leading to triphenylene III. An explanation might be given using a simplified version of the valence bond theory with a drastic reduction of the multitude of Kekulé structures to manageable proportions.

If the chemical inertness and high stability of benzene is secured by only two Kekulé structures there is no reason why there should be more Kekulé structures per benzenoid ring in fully benzenoid hydrocarbons of equal stability. There is also no reason why the double bonds in the benzenoid rings should exchange their places independently from one another, thus giving rise to a large number of structures which are not needed to explain the stability.

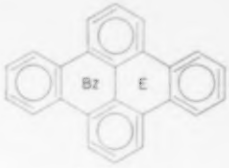
However if the movement of double bonds is synchronized in such a way that the maximum number of induced benzenoid rings (marked Bz) and a minimum number of empty rings (E) are formed, an interpretation of scheme (B) can be given. Thus triphenylene has only two Kekulé structures XVIIa and XVIIb. Only in




XVII a




XVIII a




XIX a

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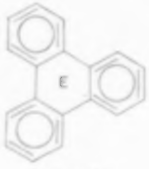


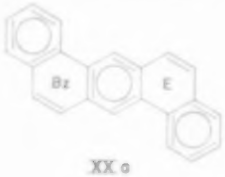

XVII b



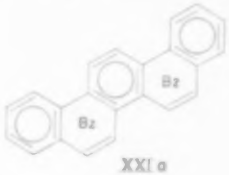

XVIII b

XIX b

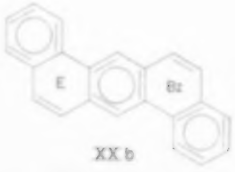
structure XVIIa are there three double bonds in the central ring which could thus have aromatic character. This is apparently not enough. In tetrabenzanthracene both structures XVIIIa and XVIIIb each have one induced benzenoid ring (Bz) and an empty ring (E). The overall benzenoidity is thus increased from 5 inherent benzenoid rings to 6. This accounts well for the fact that, according to scheme (B) a second annellation of a diphenyl system to benzene is required to produce the induced sextet. In dibenzopyrene the two Kekulé structures XIXa and XIXb have the same effect as the annellation of two *o*-phenylene systems to diphenyl.



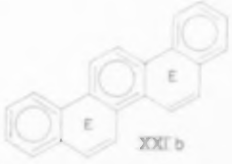

XX a




XXI a




XX b




XXI b

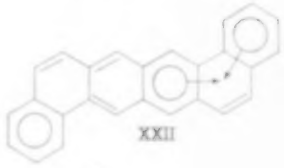
If this interpretation is correct then it should apply also in systems where two benzenoid rings are replaced by two fixed double bonds, as in XXa and XXb. Building up 1:2,5:6-dibenzanthracene XX from benzene by successive annellation of two styrene complexes results in an asymmetric annellation effect. The shift-difference rule again shows that benzene has been extended to a naphthalene system. However the agreement is not so good as that obtained on building up picene XXI in an analogous way from benzene. The difference between these two examples can only be explained by a change in the fine structure of the central ring in dibenzanthracene XX. The dibenzotetracenes XXII and XXIII and dibenzopentacenes XXIV can be obtained

XX

$\lambda_\beta = 1790$ $\xrightarrow{+720}$ 2510 $\xrightarrow{+460}$ 2970 Å
$\sqrt{\lambda_\beta} = 42{\cdot}31$ $\xrightarrow{+7{\cdot}79}$ 50·10 $\xrightarrow{+4{\cdot}40}$ 54·50 $\sqrt{\text{Å}}$
50·10 − 4·40 = 45·70 $\sqrt{\text{Å}}$ ≙ 2089 Å
$\beta$ – Band of Naphthalene, found 2210 Å

XXI

$\lambda_\beta = 1790$ $\xrightarrow{+720}$ 2510 $\xrightarrow{+335}$ 2845 Å
$\sqrt{\lambda_\beta} = 42{\cdot}31$ $\xrightarrow{+7{\cdot}79}$ 50·10 $\xrightarrow{+3{\cdot}25}$ 53·35 $\sqrt{\text{Å}}$
50·10 − 3·25 = 46·85 $\sqrt{\text{Å}}$ ≙ 2195 Å
$\beta$ – Band of Naphthalene, found 2210 Å

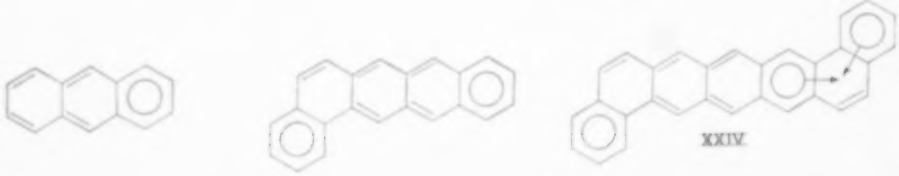


XXII

XXIII

$\lambda_\beta = 2210$ $\xrightarrow{+690}$ 2900 → 3255 Å
$\sqrt{\lambda_\beta} = 47{\cdot}01$ $\xrightarrow{+6{\cdot}85}$ 53·86 → 57·05 $\sqrt{\text{Å}}$
→ 3260 Å
→ 57·10 $\sqrt{\text{Å}}$

53·86 − 3·19 = 50·67 $\sqrt{\text{Å}}$ ≙ 2567 Å
53·86 − 3·24 = 50·62 $\sqrt{\text{Å}}$ ≙ 2562 Å
$\beta$ – Band of Anthracene, found 2534 Å (corrected for Benzene soln.)



XXIV

$\lambda_\beta = 2515$ $\xrightarrow{+675}$ 3190 $\xrightarrow{+315}$ 3505 Å
$\sqrt{\lambda_\beta} = 50{\cdot}10$ $\xrightarrow{+6{\cdot}34}$ 56·49 $\xrightarrow{+2{\cdot}71}$ 59·20 $\sqrt{\text{Å}}$

56·49 − 2·71 = 53·78 $\sqrt{\text{Å}}$ ≙ 2892 Å

$\beta$ – Band of Tetracene, found $\left\{\begin{matrix}2930\\2740\end{matrix}\right\}$ ≙ 2865 Å (corrected for Benzene soln.)
Alc. soln.

by asymmetric annellation from naphthalene and anthracene respectively. The shift-difference rule gives the correct answer in all three cases.

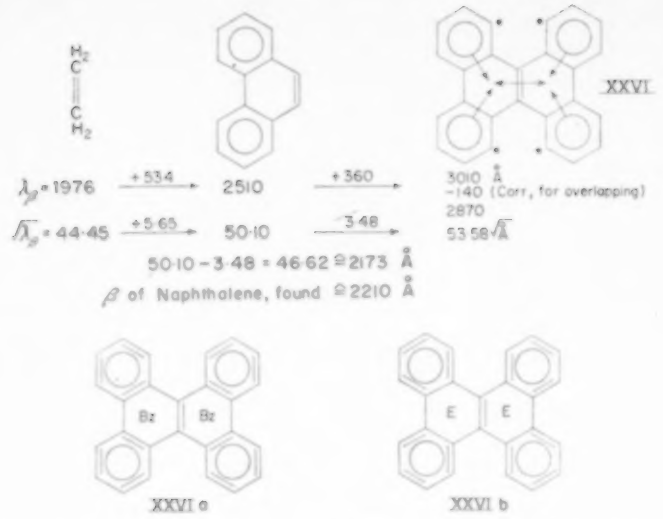
Chrysene XXV can be derived in an analogous way from ethylene. It is remarkable that the first shift (234 Å) is a small one because the newly formed ring in naphthalene has induced benzenoid character. The magnitude of the second shift is influenced by the transformation of the structure XXVa to XXVb. The latter contains a diphenyl system whose transfer to the two adjoining rings produces two fused naphthalene systems and no empty ring. The shift-difference rule gives correct figures for the $\alpha$- and $\beta$-bands of benzene even in this extreme case.

Building up tetrabenzonaphthalene XXVI in an analogous way follows a different course. The first annellation produces a big shift and an empty middle ring in phenanthrene. The second shift is much smaller. To measure it correctly the $\beta$-band of tetrabenzonaphthalene must be corrected in order to account for the over-lapping H atoms (marked by x) which shifts the $\beta$-band to the red.[2] The comparison of the $\beta$-band of chrysene with the $\beta$-band of the isomeric 3:4-benzophenanthrene which has two overlapping H atoms shows a red-shift of 140 Å. This is the minimum correction which has to be applied. Using this corrected $\beta$-band, the deduction rule gives a $\beta$-band at 2173 Å, which is very near to the $\beta$-band of naphthalene (at 2210 Å in alcohol). A bigger correction for over-lapping would give an even closer agreement. It is thus obvious that in the second annellation two induced benzenoid rings (Bz) have been formed in the centre. The central double bond must therefore participate in both central sextets.

It is already somewhat difficult to explain the asymmetric annellation effect leading to picene on the basis of the two structures XXIa and XXIb, one with two induced sextets and the other with none. But it can be claimed that on average there is only one induced sextet. However, this explanation fails in the case of tetrabenzonaphthalene. Neither with the structure XXVIa and XXVIb nor in any other pair of structures can two induced sextets on the average be obtained. It is obvious that the limit of application of the simplified valence bond scheme is reached.

The role of the double bond between two rings must be more closely defined.

[2] E. Clar and D. G. Stewart, *J. Amer. Chem. Soc.* **74**, 6235 (1952).



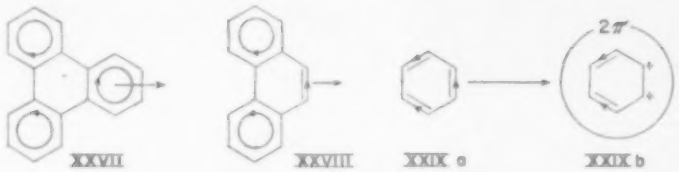

This can be done by identifying it with the transferable pair of electrons which can migrate through an acene and participation of which in the formation of an induced sextet is essential.[1] Since there is only one mobile pair of these electrons available in one inherent benzenoid ring, the central ring in picene XXI can only produce one induced sextet in one of the adjoining rings. In tetrabenzonaphthalene XXVIa the four inherent benzenoid rings and the central double bond provide five pairs of electrons symbolized by the five double bonds between the rings which form a system of five fused naphthalene complexes.

The assumption of a transferable pair of electrons symbolized by arrows becomes a necessity because the aromatic sextets alone do not indicate the asymmetry of the annellation and cannot predict in which of the two stages the formation of the first induced sextet takes place. The Kekulé structures alone can do this, but do not show the asymmetry of the annellation because both methods can give only the answer which is inherent in the choice of the symbols.

In order to understand why no induced aromatic sextet is formed in triphenylene it is necessary to define where the two transferable electrons, which have a greater mobility than the other $\pi$-electrons, are located in a benzenoid ring. If one electron rotates around the whole ring above the molecular plane the other electron must rotate in the opposite sense, below the plane. Although the momenta are compensated within the ring, there are two different ways to combine them with another electron pair of this kind in another ring. The interchange between these two pairs can be bonding or antibonding. In the ground state they will be bonding in diphenyl but it is not possible to add a third ring with a bonding pair of these electrons as in triphenylene. The situation can be best illustrated by marking the momenta of the electrons only on one side of the molecule (XXVII) because on the other side the momenta are exactly opposite. A coupling between the three pairs of electrons is just as impossible as the coupling of the rotation of three wheels touching each other. The result is that the third ring tends to be repelled by the other two, as indicated by the straight arrow in XXVII. This causes a big red-shift with no reduction produced

by an aromatization of the central ring. The bond distance between the three rings should be intermediate between a single bond in diphenyl and two single bonds of the paraffinic type.

This repulsion of the third ring is counteracted by the additional rings in tetrabenzanthracene XVIII and dibenzopyrene XIX and the formation of an induced sextet can take place.




XXVII XXVIII XXIX a XXIX b

The situation is quite similar in phenanthrene XXVIII except that one ring is replaced by one double bond. It had been shown at the beginning of this paper that a benzenoid ring can be replaced by a fixed double bond with little effect on the $\beta$-band and the asymmetric annellation. It must be concluded that a double bond can be substituted for a benzenoid ring in the interaction between benzenoid rings. This leads necessarily to the assumption that in a double bond one $\pi$-electron is above and the other below the molecular plane, both having opposed orbital momenta. This being the case the interaction of cyclic conjugated double bonds must be analogous to that between benzenoid rings.

In a Kekulé structure XXIXa there must be one double bond, antibonding relatively to the other two. Accordingly, Kekulé benzene, an alternant hydrocarbon in terms of marked carbon atoms, becomes a nonalternant hydrocarbon in terms of marked double bonds. Since the space in benzene is more limited than in triphenylene a relief of the strain is obtained by transferring two $\pi$-electrons out of one double bond to a higher level, where they belong to the ring as a whole and to no particular double bond. The remaining two double bonds can then move into any position which is the most favourable in a particular derivative. In XXIXb they receive more positive charge than in XXIXa which accounts for the extra aromatic energy in comparison with a single Kekulé structure.

There are also two electronic levels as in Hückel's term scheme,[3] the difference being that in the latter case the lowest level is occupied by two and the next higher by four $\pi$-electrons, whilst in XXIX the inverse distribution is applied, thus creating only two particularly mobile $\pi$-electrons which can migrate from one ring to another through the whole length of an acene. This gives mobility to the "background" double bonds within their rings and to the positive charges through the whole length of an ocene. It also accounts for the asymmetric annellation effect, because the pair of transferable electrons can be effective only on one side of an acene simultaneously.

[3] E. Hückel, *Grundzüge der Theorie der ungesättigten and aromatischen Verbindungen* p. 71. Verlag Chemie (1938).

Tetrahedron, 1960, Vol. 9, pp. 210 to 229. Pergamon Press Ltd. Printed in Northern Ireland

# THE INTERPLAY OF STERIC AND ELECTRONIC FACTORS AFFECTING GEOMETRICAL ISOMERISM OF DIARYL KETIMINE DERIVATIVES

P. A. S. SMITH and E. P. ANTONIADES*
Dept. of Chemistry, University of Michigan, Ann Arbor, Michigan

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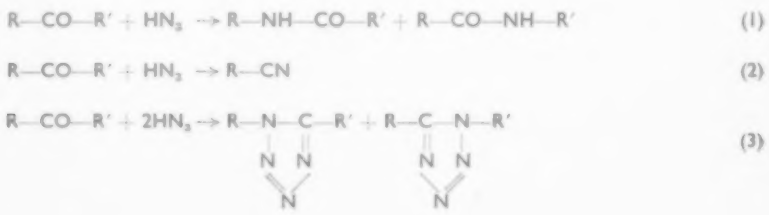
**Abstract**—The evidence bearing on the mechanism of the Schmidt reaction with ketones is critically reexamined. It is shown that dehydration of an initially formed azidohydrin (I) to a ketiminodiazonium ion (II), which may or may not equilibrate between its geometrically isomeric forms (IIa or b), can account for the various reported ratios of isomeric amides produced from unsymmetrical ketones. The previously anomalous behavior of *ortho*-substituted diaryl ketones can be resolved by taking into account the influence of conjugative effects on the preferred rotational positions. The ratios of amides produced from a series of *o*-alkylbenzophenones by both the Schmidt reaction and oximation plus Beckmann rearrangement have been determined at different temperatures; there are appreciable differences in the product ratios and their temperature coefficients from the two reactions.

IN 1948 one of us proposed[1] a mechanism for the Schmidt reaction[2] between hydrogen azide and ketones, which in the ensuing decade has been the basis for most discussion of the reaction. So much pertinent experimental investigation and theoretical discussion has since been published that a reconsideration of the overall picture seems justified at this time.

The principal reaction products of ketones and hydrogen azide are amides, of which a single compound is produced from symmetrical ketones, but a pair of isomers may be produced in unequal amounts from unsymmetrical ketones. In addition, there have been found, to an extent varying strongly with both structure and reaction conditions, nitriles, 1,5-disubstituted tetrazoles, ureas, and 5-aminotetrazole derivatives; the first of these requires one mole of hydrogen azide, the second two, two moles, and the last requires three moles for formation.



(1)



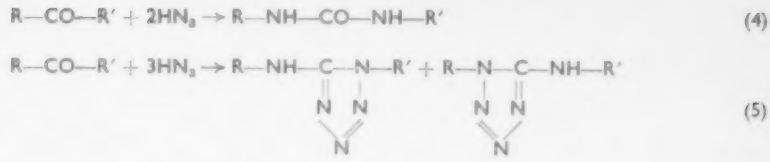
(2)



(3)

* From the doctoral dissertation of E. P. A., University of Michigan, 1957.

[1] P. A. S. Smith, *J. Amer. Chem. Soc.* **70**, 320 (1948).
[2] H. Wolff, *Organic Reactions* (R. Adams, Editor-in-Chief), Vol. III. John Wiley, New York (1946).



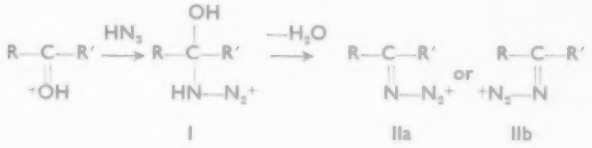
(4)

(5)

With the exception of tetrazoles originating from nitriles, the products derived from more than one mole of hydrogen azide cannot be obtained from the compounds whose formation consumed less hydrogen azide, under the conditions used in Schmidt reactions. Reactive intermediates are therefore involved, which under appropriate conditions have the choice of reacting with more hydrogen azide or of reacting in another way to give terminal products.

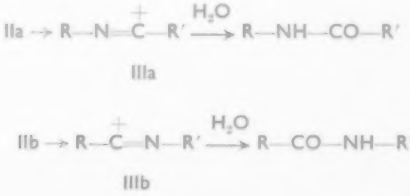
The mechanism originally referred to[1] embraces the foregoing essential facts, satisfactorily, as has been developed in subsequent publications.[3] On the other hand the reason for the observed ratios of isomeric amides from unsymmetrical ketones has been a perplexing problem, which has brought forth successively more drastic modifications of the original proposal. This paper is addressed largely to this aspect of the reaction.

Until recently there has been general acceptance of the view that the Schmidt reaction proceeds by combination of the conjugate acid of the ketone with molecular hydrogen azide to produce a protonated azidohydrin (I), which loses water to form an iminodiazonium ion (II a and b), capable of assuming two geometrically isomeric configurations when R and R′ are different. The reasonable assumption that rearrangement occurs at this stage by migration of the group *anti* to the diazonium



I IIa IIb

nitrogens provides a means whereby steric factors may influence the isomer ratio of the amides ultimately formed. The relative populations of IIa and IIb as formed



IIIa IIIb

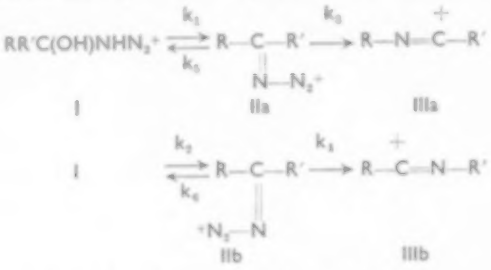
from the ketone may be presumed to be largely the result of different steric repulsions in the transition states leading to these two configurations, if there is no opportunity for thermodynamic equilibration. The ratio of populations would in turn determine

[3] P. A. S. Smith, *J. Amer. Chem. Soc.* **76**, 436 (1954).

the isomer ratio of the rearrangement products, *if the rates of rearrangement are appreciably faster than interconversion of the two configurations.*[*]

There is an extensive parallel between the ratios of isomeric amides produced in a Schmidt reaction and the equilibrium ratios of geometrically isomeric oximes formed from the same ketones. Furthermore, the ratios of these oxime isomers (usually determined by examination of the amides formed from them by Beckmann rearrangement) are largely in accord with the generalization that the more stable configuration is that in which the bulkier group is *anti* to the oxime hydroxyl,[4] and are not influenced by the electronic effects that determine migration aptitudes.[5] The ratios of amides produced by the Schmidt reaction have been shown to have a similar relation to structure.[6] To the extent that these generalizations are valid, one can deduce from them that the italicized condition in the foregoing paragraph is satisfied, and that "migration aptitudes" do not therefore determine the isomer ratios in the product.

[*] The reaction sequence from the protonated azidohydrin, I, to the iminocarbonium ions, IIIa and IIIb, comprises two parallel paths, each of which at constant acidity is a sequence of a pseudo-first-order and a first-order reaction, the first step of which may be reversible, while the second step is irreversible.



Once IIIa and IIIb are formed, the ratio of isomeric amides derived from them is determined, and we need not here be concerned with their precise fate. If the first steps are reversible and faster than the second steps, thermodynamic equilibrium between IIa and IIb is attained, and $IIa/IIb = K = k_1k_6/k_5k_3$. (The same thermodynamic equilibrium might of course be reached by other paths, notably through protonation of IIa and IIb to form $RR'\overset{+}{C}—NH—N_2^+$, but this would not affect the ratio IIIa/IIIb). It can be shown that in this case the ratio IIIa/IIIb is given by $K \cdot k_2/k_4$. The practical result would be that the ratio of amides ultimately obtained would be determined as much by the relative migration aptitudes ($k_2/k_4$) as by the relative stability of geometrical isomers IIa and IIb.

If, on the other hand, IIa and IIb should not interconvert faster than they rearrange, the first steps could be treated as irreversible, and thermodynamic equilibrium would not be attained. The rate expressions in this case are

$$d(IIa)/dt = k_1(I) - k_5(IIa)$$
$$d(IIb)/dt = k_5(I) - k_4(IIb)$$
$$d(IIIa)/dt = k_3(IIa) = k_1(I) - d(IIa)/dt$$
$$d(IIIb)/dt = k_4(IIb) = k_5(I) - d(IIb)/dt.$$

By dividing the integrated forms of the latter two we obtain the time-dependent expression

$$\frac{(IIIa)}{(IIIb)} = \frac{k_1\int(I)dt - (IIa)}{k_5\int(I)dt - (IIb)}$$

for the ratio of the products. It follows readily that the limiting ratio for $t = \infty$ is $k_1/k_5$, and by the successive application of l'Hospital's rule the limiting ratio for $t = 0$ is found to be $k_3k_5/k_2k_4$. If the transition states for the first steps (dehydration) resemble the products appreciably, $k_1$ and $k_5$ would be approximately proportional to the thermodynamic stabilities of IIa and IIb, and the factors governing the relative stability of the geometrical isomers would operate to determine the ratio of amides obtained, and a parallel between the Schmidt reaction ratios and oximation ratios would be expected, in agreement with the results generally observed. The parallel would be expected to be only approximate, however, since thermodynamically controlled ratios in oximation are being compared with kinetically determined ones in the Schmidt reaction.

[4] A. D. McLaren and K. E. Schachat, *J. Org. Chem.* **14**, 254 (1949).
[5] W. E. Bachmann and M. X. Barton, *J. Org. Chem.* **3**, 300 (1938).
[6] [a] P. A. S. Smith and J. P. Horwitz, *J. Amer. Chem. Soc.* **72**, 3718 (1950); [b] H. Schechter and J. C. Kirk, *Ibid.* **73**, 3087 (1951); [c] R. Fusco and S. Rossi, *Gazz. Chim. Ital.* **81**, 511 (1951); [d] R. T. Conley, *Chem. & Ind.* 438 (1958).

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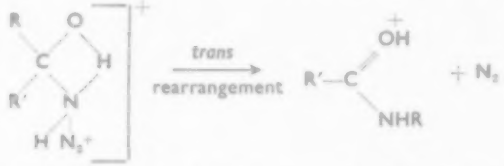
They also support the contention that the ratio of *syn* and *anti* configurations of the iminodiazonium ion (II) is roughly proportional to their relative stabilities, even though the ratio may be kinetically determined.[7] That is, the two transition states for dehydration of I to IIa and IIb resemble the products, and their relative energies may be approximated by those of IIa and IIb.

The most bothersome exceptions to these generalizations have been observed among benzophenones. Many benzophenones substituted in an *ortho* position[9] give ratios of amides and oxime ratios that imply that the more stable configuration has the *ortho*-substituted phenyl group *syn* to the N-attached hydroxyl or diazonium group. In another case, *p*-methoxybenzophenone, the usually ineffective migration aptitudes appear to operate to a limited extent in the Schmidt reaction, although they do not in *p*-methoxy-*p'*-nitrobenzophenone.[6a,10] Finally, a few benzophenones appear to give ratios of amides from the Schmidt reaction that are measurably different from those of the equilibrated oximes.[9c]

An attempt was recently made by Arcus, Coombs and Evans[11] to resolve these anomalies by postulating a substantially different path for the Schmidt reaction, not involving dehydration of I to an iminodiazonium ion (II). Their proposal features a four-membered chelate ring that undergoes rearrangement entirely intramolecularly to give the conjugate acid of an amide directly. Geometrical isomerism would be possible in this ring intermediate if the bonds about the ring nitrogen have a pyramidal arrangement, and this is presumed to account for the ratios of product isomers.




We do not believe this proposal offers a more satisfactory explanation of the observed amide ratios, inasmuch as the attractive and repulsive effects that determine configuration operate between the same groups in the chelate ring intermediate as in the iminodiazonium ion (or the transition states leading to it). Apart from this, however, there are other objections to this intermediate. It is unlikely that such a ring intermediate could satisfy the condition that equilibration between its geometrical isomers be slow, since the energy of the hydrogen bond that completes the ring must be extremely small at the strained angle of a four-membered ring. Furthermore, such an intermediate provides no path for the formation of the other products, such as tetrazoles, sometimes produced in Schmidt reactions, and destroys the mechanistic similarity between the Schmidt reaction and the Beckmann rearrangement.

Experimental support for the ring intermediate has been offered in the form of a Schmidt reaction on fluorenone in which the reaction mixture was worked up by first being poured into methanol; phenanthridone was formed as usual, and no

[7] That the dehydration step (and its reverse) is probably a slow one is suggested by Jencks' observations that in the analogous oximation process, the carbonyl-hydroxylamine adduct is formed rapidly, but dehydrates to the oxime slowly.[8]

[8] W. P. Jencks, *J. Amer. Chem. Soc.* **81**, 475 (1959).

[9] [a] G. M. Badger, R. T. Howard and A. Simons, *J. Chem. Soc.* 2849 (1952); [b] J. R. Dice and P. A. S. Smith, *J.Org. Chem.* **14**, 179 (1949), [c] P. A. S. Smith, *J. Amer. Chem. Soc.* **76**, 431 (1954).

[10] P. A. S. Smith and B. Ashby, *J. Amer. Chem. Soc.* **72**, 2503 (1950).

[11] C. L. Arcus M. M. Coombs and J. V. Evans, *J. Chem. Soc.* 1498 (1956).

9-methoxyphenanthridine was detected. It was argued that the concentrated sulfuric acid constituting the reaction medium would "be unlikely to liberate the water" required to convert iminocarbonium ions (III) to amides, and that their procedure should therefore have produced 9-methoxy-phenanthridine if the mechanism actually involved the formation of an iminocarbonium ion. Since only phenanthridone was produced, they concluded that neither iminocarbonium ions nor their necessary precursors, iminodiazonium ions, are formed during the Schmidt reaction. We believe these arguments to be invalid.

The successful substitution of alcohols for water as the nucleophile taken up by the reactive intermediate in the Schmidt reaction has been known for a long time from the work of Schmidt and others,[12] who prepared imino esters by treating ketones with hydrogen azide and hydrogen chloride in alcohol solution (9-methoxy-phenanthridine is but a special example of an imino ester). The difference between these experiments and those of Arcus *et al.* is that the earlier Schmidt reactions took place in the presence of alcohols, while alcohol was not introduced by Arcus *et al.* until the Schmidt reaction was completed. The latter circumstances allowed the iminocarbonium ion to acquire the elements of water from the environment, presumably by initial reaction with bisulfate ion, notwithstanding the fact that this was nearly 100 per cent sulfuric acid. The ability of iminocarbonium ions to extract water from concentrated sulfuric acid is demonstrated by the well known general procedure for hydrating nitriles to amides by simply warming them with sulfuric acid. Furthermore, if the iminocarbonium ion were thermodynamically incapable of abstracting water from sulfuric acid, we might expect that amides would be dehydrated by that reagent, in contrast to their known stability in sulfuric acid solutions. In addition, Newman and Deno attempted to obtain cryoscopic evidence for the formation of iminocarbonium ions from amides of favorable structure, but failed.[13] The evidence, then, is definitey contradictory to the chelate ring intermediate, and is consistent with the formation of an iminocarbonium ion; we thus find ourselves returned to the mechanism proposed in 1948.

In order to seek insight into the reasons for the anomalous isomer ratios of the amides from *o*-substituted benzophenones, we began our investigations with a careful repetition of the Schmidt reaction and of the oximation of *o*-methylbenzophenone. We at first hoped to be able to prepare pure samples of the *syn* and *anti* oximes of a series of *o*-alkyl benzophenones and to determine their respective absolute entropies by heat capacity measurements from room temperature down to liquid helium temperatures. The preparation of one isomer of *o*-methylbenzophenone by oximation under but mildly basic conditions, of the other by oximation in hot, strong alkali has been reported by Smith.[14] Similar observations have been reported for 1-benzoyl-naphthalene by Betti and Poccianti.[15] Repeated attempts to confirm these reports failed in our hands, and we believe that the earlier workers may have been misled by samples of different purity, or may have mistaken a eutectic mixture for a single isomer. Attempts to separate the isomeric oximes from the equilibrium mixtures by fractional crystallization or by chromatography gave only the major isomers in pure form.

[12] e.g., K. F. Schmidt and P. Zutavern, U.S. Pat. 1,889,323; *Chem. Abstr.* **27**, 1361 (1933).
[13] M. S. Newman and N. C. Deno, *J. Amer. Chem. Soc.* **73**, 3651 (1951).
[14] A. W. Smith, *Ber. Dtsch. Chem. Ges.* **24**, 4047 (1891).
[15] M. Betti and P. Poccianti, *Gazz. Chim. Ital.* **45 II**, 224 (1915).

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Our next approach, after we found we could not obtain the pure isomeric oximes in this series, was to determine the ratios of oxime isomers formed at two temperatures, 60° and 118°, in order to estimate from them the magnitude and sign of the differences between the thermodynamic properties of the isomers. The ratios were determined by carrying out Beckmann rearrangements on the mixtures and analyzing the resulting mixtures of amides by infrared spectroscopy.

The results are given in Table 1. It can be seen that an increase of temperature favors the minor isomer, but that the magnitude of the effect varies with the nature of the alkyl group in *o*-alkyl benzophenones. The low precision of measuring the ratios when they are so far from 1 : 1 unfortunately prevents the calculation of reliable thermodynamic constants from them. These data do show the importance of the temperature variable, which must be taken into account when attempting to interpret ratios reported by different investigators; temperatures used in oximation or the Beckmann rearrangement are seldom reported or carefully controlled. Similar temperature effects in the Schmidt reaction on other ketones have been reported by Schechter and Kirk.[6b]

Table 1 also includes the ratios of amides produced by the Schmidt reaction, carried out at 60° to allow comparison with the oximation ratios. While these results

TABLE 1. ISOMER RATIOS FROM OXIMATION AND FROM THE SCHMIDT REACTION OF KETONES Ar–CO–$C_6H_5$

| Ar | Oximation plus Beckmann rearrangement | | | | Schmidt reaction | |
|---|---|---|---|---|---|---|
| | At 60° | | At 118° | | At 60° | |
| | Yield of amides, %[a] | Migration ratio, Ar:$C_6H_5$ | Yield of amides, % | Migration ratio, Ar:$C_6H_5$ | Yield of amides, % | Migration ratio, Ar:$C_6H_5$ |
| *o*-Tolyl | 93 | 15·5:84·5 | 98 | 22:78 | 80·5[b] | 22:78 |
| | | | | | 99 | 23·5:76·5 |
| *o*-Ethylphenyl | 92·5 | 5:95 | 97 | 28:72 | 80·5[c] | 21:79 |
| | | | | | 95·5 | 23:77 |
| *o*-Isopropylphenyl | 75[d] | 13·5:86·5 | 98·5 | 28:72 | 93·5 | 18:82 |
| | | | | | 96 | 17·5:82·5 |
| *o*-t-Butylphenyl | | | | | 1·2[e] | ~70:30 |
| α-Naphthyl | | | 95·5 | 18:82 | 98 | 30:70 |

[a] Overall yield from ketone by oximation followed by Beckmann rearrangement. [b] Plus 13% recovery of ketone. [c] Plus 16% recovery of ketone. [d] Plus 20% recovery of ketone. [e] Plus 95·5% recovery of ketone.

support the generalization that the Schmidt reaction and oximation plus Beckmann rearrangement give similar ratios of isomeric amides, they also show that the agreement is only qualitative. There are small but significant differences; furthermore, the direction of the differences depends on the temperature of oximation chosen for comparison, and a temperature must therefore occur in the relatively short range of 60–118° where the oximation ratios would be essentially the same as the amide ratios from the Schimdt reaction at 60°. Differences of this magnitude are thus so strongly influenced by the various temperature coefficients that a simple interpretation of them in terms of temperature-invariant steric and electronic repulsions would be naive.

A feature of significance is that there is very little difference in the isomer ratios of the products whether the *o*-alkyl substitutent is methyl, ethyl or isopropyl. (t-Butyl is questionable, since *o*-t-butylbenzophenone was found to be so extremely unreactive that no oximation could be detected, and Schmidt reaction occurred to only a minute extent, even under forcing conditions.) This insensitivity to the size of the *ortho* substitutent is also found in the *o*-halobenzophenones, which give almost the same ratios of amides by the Schmidt reaction as do the *o*-alkylbenzophenones.

There appear to be two ways by which the near-constancy in the isomer ratios of amides obtained from *o*-alkyl and *o*-halo benzophenones by the Schmidt or Beckmann reactions may be accounted for. The absence of appreciable influence of migration aptitudes and the general stereospecificity with respect to oxime configuration make it reasonably certain that we have to deal with the geometrical isomerism of ketimine derivatives rather than the rearrangement step.* One possibility that the effects due to changes in the size of the *ortho*-substitutent are balanced by differences in their electronic influence. Such an explanation requires a coincidence in the balance of the two effects that is highly improbable, expecially in view of the known difference of electronic character between halgens and alkyl groups of comparable size. The other possibility is that any substitutent appreciably larger than hydrogen might be sufficient to enforce the observed preferred configuration, and that further increases in size would be without appreciable effect, unless a threshold size should be reached where additional configurational changes are imposed. Such a set of circumstances would

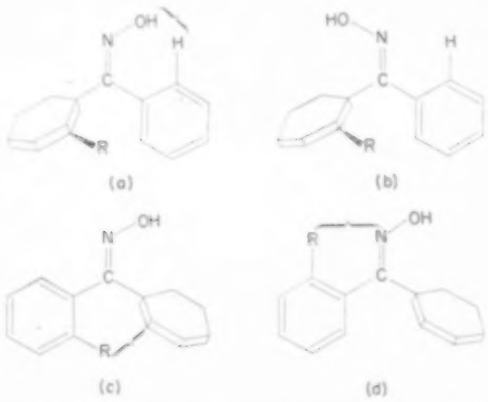


FIG. 1. Interference in some rotational conformations of *ortho* substituted benzophenone oximes.

* The discussion of the conformation of the ground states of the geometrical isomers of oximes or analogs may raise the question of their relation to the transition state for rearrangement. If the transition state is properly represented by a bridged structure, R—C=N—T, it would be expected to be of lowest energy, in the case of a migrating aryl group, when the plane of the benzene ring is perpendicular to the C—N axis. The conformations represented by B, C and D in Fig. 1 would thus have to undergo rotation of the *anti*- arylgroup as the transition state is approached, incidentally destroying the conjugation that stabilized the ground-state conformation. However, strict perpendicularity is by no means essential, as demonstrated by the readily successful Beckmann and Schmidt reactions of fluorenone, where a large departure from coplanarity would be resisted by the ring structure. The presence or absence of rotation accompanying rearrangement might be reflected in the activation energies, but would not affect the argument given here.

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not be unreasonable if the effect of the substitutent should be to prevent rotation or coplanarity in a critical part of the system.

Scale models of benzophenone derivatives show that an *ortho*-substituent hinders the substituted ring from being coplanar with an oxime function [or the iminodiazonium intermediate (II)]. This in turn interferes with the substituted ring being in conjugation with the carbonyl derivative,[16] with the result that the favored configuration would be that shown (for oximes) in Fig. 1B, in which the two benzene rings have their perpendicular axes skew to each other, and only the unsubstituted ring is in conjugation. In the case of an oxime or iminodiazonium ion, such a rotational position disposes the carbonyl derivative to have its more stable configuration *anti* to the unsubstituted phenyl group, owing to interference between the hydrogen in the outer, up-ended *ortho* position and the hydroxyl or diazo group on the nitrogen.

The effects just delineated consider the *ortho*-substituent solely as a source of steric hindrance. If, in addition, the substituent is of such electronic character as to promote conjugation, then a conflicting influence is present. Configuration D. (Fig. 1), which allows the *ortho*-substituted phenyl group to be in conjugation with the C=N system with the smallest amount of interference, is the geometrical isomer opposite to that in configuration B. The resulting equilibrium would be a balance between the simple bulk effect, leading to the *syn*-configuration, and the promotion of conjugation, leading to the *anti* configuration. Such a situation may be met in *o*-methoxybenzophenone, which has been shown to produce roughly equal amounts of the two isomeric amides formed in the Schmidt reaction, and we are thus able to account for the different effect on the isomer ratios of *o*-ethyl and *o*-methoxy, whose steric requirements are not very different.*

An *ortho* or *para* methoxy group causes another effect through its electronic influence. Hauser and Vermillion[17] have described a study of the influence of substituents on the interconversion of stereoisomeric benzaldoximes, and have shown that the methoxy group promotes it. In view of this, it is not unreasonable to expect that the rate of interconversion of the stereoisomers of methoxybenzophenone derivatives might become comparable to the rate of rearrangement, thus allowing migration aptitudes to make their influence felt (cf. paragraph 5). Support for this view in the particular case of *o*-methoxybenzophenone is found in the report that although its two isomeric oximes can be separated, one isomer is considerably more stable than the other. Interconversion occurs under unusually mild conditions. Beckmann rearrangement of either isomer gives principally benzo-*o*-anisidide.[18] Since the amides from the Schmidt reaction consist of 50 per cent of this isomer, we see that in both the Beckmann and Schmidt rearrangements migration of the *o*-anisyl group occurs to a very substantially larger extent than of *o*-alkyl- or *o*-halophenyl. Although we cannot from these facts alone tell whether this is the result of the steric effect as influenced by conjugation or of the partial operation of migration aptitudes, a combination of both seems most likely.

It is fruitful in this connection to re-evaluate the observations reported for *p*-methoxybenzophenones, in which the steric effect of an *ortho* substituent is missing,

* The methoxyl group actually has somewhat smaller steric requirements than the ethyl group, since the effective radius of ether oxygen is less than that of methylene.

[16] H. H. Szmant and C. M. Harmuth, *J. Amer. Chem. Soc.* **81**, 962 (1959); R. N. Jones, *Ibid.* 67, 2141 (1945).
[17] C. R. Hauser and G. Vermillion, *J. Amer. Chem. Soc.* 63, 1224 (1941).
[18] [a] P. Billon, *Ann. Chim.* [10], 7, 341 (1927); [b] M. Martynoff, *Ibid.* [11], 7, 424 (1937).

but the electronic influence and migration aptitude are retained. *p*-Methoxybenzophenone should show equal extents of phenyl and *p*-anisyl migration in the Schmidt reaction if only simple steric effects operate. Nevertheless, it has been reported[6a] and independently substantiated[19] that migration of the *p*-anisyl group occurs preferentially to the extent of nearly 2 : 1. This can be interpreted as evidence that migration aptitudes have come into play. There are, however, two other *p*-methoxybenzophenones whose Schmidt reactions have been studied; they are the *p'*-chloro and *p'*-nitro derivatives. The addition of either of these substituents returns the ratio of migration to the statistical value, 1 : 1, and thus eliminates the effect observed in *p*-methoxybenzophenone. This result is understandable in the light of the work of Chapman and Fidler[20] on the relative rates of migration of substituted phenyl groups in the Beckmann rearrangement of benzophenone oximes, in which they showed that electron-withdrawing substituents on the non-migrating phenyl group noticeably decrease the rate of rearrangement of the other group. It is also to be presumed that such substituents would decrease the rate of equilibration between the *syn*- and *anti* forms of the iminodiazonium ion, analogous to the effect observed by Hauser and Vermillion of these substituents on the interconversion of benzaldoxime isomers. In both ways, therefore, the marginal operation of migrational apitudes in *p*-methoxybenzophenone would be nullified. Evidence that the preferential anisyl migration is at least partly a result of geometrical orientation appears in the characteristics of the

two *p*-methoxybenzophenone oximes. The *anti*-anisyl isomer, which gives benzaniside on rearrangement, is the more stable.[21] This is to be expected if the *p*-methoxy group should greatly stabilize a configuration analogous to Fig. 1D, by enhancing conjugation of the anisyl group with the C=N system.

There remains to be discussed a group of three *ortho*-substituted benzophenones,

[19] R. D. Westland and W. E. McEwen, *J. Amer. Chem. Soc.* **74**, 6141 (1952).
[20] A. W. Chapman and F. A. Fidler, *J. Chem. Soc.* 448 (1936).
[21] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **24**, 51 (1893).

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*o*-carboxy, *o*-nitro and *o*-phenyl, which show predominant migration of the substituted aryl group in the Schmidt reaction. The way in which this anomalous behavior can be reconciled has been pointed out by Arcus and Coombs for the first example; cyclization occurs to give a derivative of the lactol form and the rearrangement is that of an azide rather than of a ketimine derivative.* Since the nitro group and the carboxylate ion are isoelectronic, analogous behavior with *o*-nitrobenzophenone might not be unreasonable.† Evidence that such interaction occurs between nitro oxygen and the carbonyl group in *o*-nitrobenzoyl chloride has been given by Szmant and Harmuth.[16] The analogous behavior with *o*-phenylbenzophenone would lead to 9-phenyl-9-fluorenyl azide as the intermediate. The necessary postulate that this rearranges to 9-phenylphenanthridine, the observed product of the Schmidt reaction, receives strong support from the report that 9-methyl- and 9-benzyl-9-fluorenol rearrange to the 9-substituted phenanthridines through their 9-azido derivatives.

Since we have seen that the effects which once seemed anomalous in the Schmidt reaction and in oxime configuration of *o*-substituted benzophenones can be understood when the non-coplanarity of the two benzene rings is taken into account, it is especially pertinent to consider the behavior of the related derivatives of fluorenone, in which a bridged structure holds the benzene rings coplanar. Thus geometrical factors should operate in fluorenone derivatives in a way conditioned by the enforced coplanarity of the nuclear system and the $=N—O—$ or $=N—N_2^+$ in the carbonyl-derived function, distinct from the superficially similar benzophenone system. 1-Substituted fluorenones, the analogues of *o*-substituted benzophenones, are difficult to synthesize and consequently have been little investigated. An example of the oximation and Beckmann rearrangement of such a structure has been reported in the case of retene ketoxime,[22] which on rearrangement gave solely 2-methyl-8-isopropylphenanthridone. The only example of a Schmidt reaction on a 1-substituted fluorenone is that of 1,3-dimethyl-2-azafluorenone,[23] which gives 1,3-dimethyl-2-azaphenanthridone, the product formed by migration of the substituted side. It appears from these two examples that the rule of migration of the bulkiest group holds once more in an uncomplicated manner when the conformational effects which have been discussed for benzophenones are prevented by enforced coplanarity.

The behavior of 2- and 3- substituted fluorenones in the Schmidt reaction has been investigated recently, and the results have been presented as further examples of anomalies not explainable by the "greatest bulk" rule for predicting the isomeric

* An alternative explanation has been offered by M. V. Bhatt, *Chem. & Ind.* 1390 (1956), utilizing the assumption that an *o*-carboxyphenyl group would migrate preferentially to phenyl owing to the operation of the "greatest bulk" rule in the stereochemistry of the iminodiazonium ion. Apart from the fact that a mass of data shows that this rule cannot be so simply applied in benzophenone derivatives, it has been shown by C. L. Arcus and R. E. Marks, *J. Chem. Soc.* 1627 (1956), that *o*-carboxyphenyl also migrates preferentially over the presumably bulkier mesityl group, and the basis for Bhatt's explanation loses its support.

† Support for this is provided by our observation that solutions of *o*-nitrobenzophenone in sulfuric acid are initially pale yellow (owing to end-absorption of the protonated carbonyl structure), but slowly change their ultraviolet and visible spectral characteristics, becoming rosy-purple with strong blue fluorescence; similar solutions of *p*-nitrobenzophenone remain unchanged indefinitely. Dr. N. C. Deno and Mr. G. Saines of Pennsylvania State University have kindly determined the van't Hoff *i*-factor in sulfuric acid for us; it has the value 1·97 30 min after mixing, corresponding to simple protonation of the carbonyl group, but increases to 3·00 after 70 min and 5·90 after 2 days (formation of the dipositive ion that would be parent to the azide structure IV would give a theoretical i-factor of 5). It should be noted that the Schmidt reaction on *o*-nitrobenzophenone is very slow - even at 60°, so that ample time is available for the foregoing processes.

[22] D. E. Adelson and M. T. Bogert, *J. Amer. Chem. Soc.* **58**, 2236 (1936).
[23] V. A. Petrow, *J. Chem. Soc.* 200 (1946).

constitution of the products. Specifically it was determined that 2-nitrofluorenone produces 2-nitrophenanthridone, the isomer resulting from migration of the nitrated ring to nitrogen, in a ratio of 19 : 1; 2-methoxy- and 3-nitrofluorenone gave roughly equal quantities of the respective isomeric phenanthridones (the actual ratio, 69 : 31, reported for 3-nitrofluorenone, should be taken with reservation, inasmuch as it is based on only a 65 per cent yield of amides with no compensating recovery of ketone, and an analytical procedure beset with considerable uncertainties). The oximation of 2- and 3-nitrofluorenones has also been studied, but the results, contrary to the original report, do not allow a reliable estimate to be made of the ratios of isomers formed.[24] We believe the ratios observed in the Schmidt reaction in reality provide support for the "greatest bulk" rule, by which we will show they too, can be explained.

It has been pointed out (Fig. 1A) that there is interference between the oximino group (and by implication, an iminodiazonium group) and an *ortho*-hydrogen, when a *syn*-phenyl group of a benzophenone derivative is coplanar with the carbonyl-derived group. Any fluorenone oxime thus represents a slightly strained system, as a result of the enforced coplanarity, and this strain is presumably accommodated in part by a slight bending of the 1-hydrogen away from the ketoxime group. Now let us consider 2-substituted fluorenones, and particularly 2-nitrofluorenone. The ability of the molecule to accommodate the strain in the *syn*-oxime by a bending of the 1-hydrogen in the direction of the 2-position will be reduced by the bulk of any 2-substituent. This is the "buttressing effect"[25] observed in the mutarotation of optically active biphenyls. The nitro group is particularly bulky, and its bulk gives maximum buttressing effectiveness when it is coplanar with the benzene ring, the position of most effective conjugation. In this position molecular models actually show a small amount of interference between the nitro oxygen and the 1-hydrogen. The result is that the *syn*-configuration of 2-nitrofluorenone oxime should be noticeably less stable than the *anti*-configuration, and by implication the Schmidt reaction should reflect these influences by producing mostly the *anti*-configuration of the intermediate iminodiazonium ion, and from it 2-nitrophenanthridone, the major observed product. Whether a secondary buttressing effect from the 3-nitro group could be sufficiently important to affect the ratio of products from 3-nitrofluorenone is questionable.

While this paper is primarily concerned with aromatic ketones, it is necessary to consider the behavior of aliphatic ketones as well, particularly with regard to the recent report[26] that there is both a small intermolecular and intramolecular isotope effect with acetone-1 $C^{14}$. The generally good agreement with the rule of migration of the bulkier group in either the Schmidt reaction or oximation plus Beckmann rearrangement had led to an earlier conclusion that geometrical effects operated in an uncomplicated way. However, it has recently been shown that increasing alkyl substitution at the α-carbon increases migration aptitudes (or more precisely, rate of migration) in both C-to-O and C-to-C migrations,[27,28] which suggests that migration aptitudes might equally well explain the observed products in the C-to-N rearrangements. It is significant in this connection that isomeric oximes of wholly aliphatic

[24] A. J. Nunn, K. Schoefield and R. S. Theobald, *J. Chem. Soc.* 2797 (1952); K. Schoefield, private communication.
[25] W. F. Forbes and W. A. Mueller, *J. Amer. Chem. Soc.* **79**, 6495 (1957) for a summary of literature.
[26] A. Ropp, W. A. Bonner, M. T. Clark and V. F. Raaen, *J. Amer. Chem. Soc.* **76**, 1710 (1954).
[27] M. F. Hawthorne and W. D. Emmons, *J. Amer. Chem. Soc.* **80**, 6393 (1958).
[28] R. M. Stiles and R. Mayer, *J. Amer. Chem. Soc.* **81**, 1497 (1959).

ketones cannot usually be isolated, and the behavior when separation is attempted suggests extremely easy interconversion. The same factors which are responsible for this ease of interconversion of oxime isomers should also promote interconversion of the corresponding imindiazonium ion isomers, II a and b, in the Schmidt reaction. As we have already pointed out, as interconversion of the geometrical isomers of the rearranging species becomes important, so does the role of migration aptitudes in determining product ratios.* The isotope effect observed by Ropp *et al.* implies that in aliphatic ketones migration aptitudes compete with simple geometrical factors in determining the product composition, and the rule of migration of the bulkier group should not necessarily be expected to hold for those aliphatic ketones where migration aptitudes and steric effects may be opposed.

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We should like to comment on another factor influencing product ratios in the Schmidt reaction, that of reaction medium. McEwen *et al.*[29] studied the effect of the acidity of the reaction medium on the Schmidt reaction on five benzaldehydes (Table 2), and confirmed the original claim by Schmidt[30] that in the case of benzaldehyde, a

TABLE 2. PRODUCTS FROM THE SCHMIDT REACTION ON BENZALDEHYDES *p*-R—$C_6H_4CHO$ (According to McEwen *et al.*[29])

| Substituent, R— | Ratio of sulphuric acid to aldehyde | Yield, %* | |
|---|---|---|---|
| | | Nitrile | Formanilide |
| H— | 0·72 | 32 | 14 |
| | 5·4 | 10 | 59 |
| $CH_3O$— | 0·72 | 86 | 0 |
| | 5·4 | 64 | 0 |
| Cl— | 0·72 | 55 | 12 |
| | 5·4 | 15 | 48 |
| $NO_2$— | 0·72 | 72 | 2 |
| | 5·4 | 46 | 23 |
| $CH_3$— | 0·72 | 50 | 6 |
| | 5·4 | 13 | 43 |

* Yields are based on aldehyde consumed, and include all derived substances.

low ratio of sulfuric acid to aldehyde gave principally benzonitrile, while increasing acidity promoted the formation of formanilide. They interpreted this behavior on the basis of the assumption that benzonitriles arose through elimination in the *anti*-H configuration of the iminodiazonium intermediate, and that formanilides arose through aryl migration in the *syn*-H configuration. In order to account for their results in these terms, they were led to the assumption that the less stable *anti*-H configuration was formed first, i.e., more rapidly than the *syn*-H configuration. This assumption is directly opposed to the generalization proposed at the beginning of this paper, and this opposition must be resolved if we are to have a satisfactory overall concept of the operation of the Schmidt reaction.

Reference to the analogous behavior of benzaldoximes does not support the assumption that the *anti*-isomer is formed first in the Schmidt reaction, but adds strong

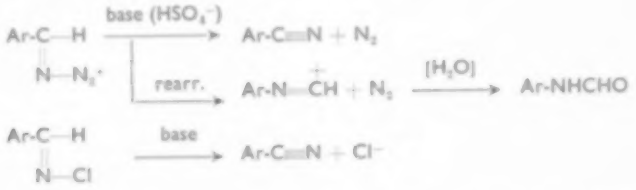
* See footnote following ref. 3.

[29] W. E. McEwen, W. E. Conrad and C. A. Vander Werf, *J. Amer. Chem. Soc.* **74**, 1168 (1952).

[30] K. F. Schmidt, D. R. P. 427,858, April 20 (1926).

support to the assumption that nitriles arise by elimination. The *syn*-H oximes have been shown to be formed first[5,31] when benzaldehydes are oximated, even under conditions of acidity where the *anti*-H salts are more stable. However, aldoxime derivatives are indeed converted to nitriles readily by treatment with bases (conditions that do not promote the Beckmann rearrangement in general).[32] It would appear that nitrile formation from aldoxime derivatives is a base-catalyzed elimination, which may occur from both the *syn*-H and *anti*-H forms, but more readily with the latter, which allows *trans* elimination. If these characteristics also hold for the Schmidt reaction on aldehydes, it is not necessary to postulate that the less stable iminodiazonium ion configuration is formed fastest, and the observed facts can be accounted for in terms of an extension of the elimination concept. Elimination from Ar-CH=N—$N_2^+$ (Schmidt reaction intermediate) would be expected to be a far easier process than from Ar-CH=NOAc (oxime derivative), since the positive charge would promote the acidity of the hydrogen, and molecular nitrogen is a much better leaving group than carboxylate anion; it might even under some conditions become an $E_1$ process.

In the sulfuric acid-catalyzed Schmidt reaction, the principal base available to remove the aldehyde hydrogen and so form a nitrile is bisulfate ion. At low ratios of sulfuric acid to benzaldehyde and in the presence of sodium bisulfate, elimination could occur more readily than at the higher ratios, at which the formation of formanilides was found to be promoted. With elimination suppressed by the higher acidity, the usual Schmidt rearrangement becomes more important, and since the *syn*-H configuration, being the more stable, is predominantly present, aryl migration ensues to produce formanilide.




Two of the substituents, nitro and methoxy, had marked effects on the ratio of nitrile to formanilide formed, each promoting nitrile formation. The effect of the nitro group is easily attributed to an increase in the acidity of the eliminated hydrogen, and is in agreement with published observations of the effect of substituents on other eliminations, of which the kinetic study of the base-catalyzed elimination (presumably *cis*) from N-chlorobenzaldimines (presumably *syn*-H) is perhaps the most pertinent,[33] and also to the retarding effect of the nitro group on aryl migration.

The reported effect of the methoxy group is anomalous, since this group usually retards eliminations. An explanation for depressed aryl migration, but not the complete absence of it, can be developed from a consideration of the effect of the methoxy group in *p*-methoxybenzophenone; as has been discussed in an earlier section, enhanced migration of the anisyl group is observed, and may result in part from the ability of the *p*-methoxy group to promote acid-catalyzed interconversion

[31] H. Lindemann and K.-T. Tschang, *Ber. Dtsch. Chem. Ges.* **60**, 1725 (1927).
[32] J. Meisenheimer and W. Theilacker, *Stereochemie* (Edited by K. Freudenberg), p. 974 *et seq.* Franz Deuticke, Leipzig (1932).
[33] C. R. Hauser, J. W. Le Maistre and A. E. Rainsford, *J. Amer. Chem. Soc.* **57**, 1056 (1935).

between *syn* and *anti* forms. Since the *anti*-H form of the iminodiazonium ion would be expected to undergo *trans*-elimination very much faster than *cis*-elimination from the *syn*-H form, a path would thereby be opened for nitrile formation to prevail markedly over formanisidide formation by aryl migration. Elimination via the less stable *anti*-H form would add only a small amount to the energy barrier, inasmuch as the energy difference between the *syn* and *anti* forms of aldoximes has been found to be of the order of 1 to 2 kcal.[24] Furthermore, increasing acidity of the medium, which for most benzaldehydes retards elimination, would in this case have in addition a counteracting effect, in the form of accelerating the interconversion to the much more rapidly eliminating *anti*-H form. In this way also, the intrinsically greater ability of the anisyl group to migrate would be overridden. The foregoing interpretation receives additional support from the fact that neither *syn*- nor *anti*-anisaldoxime undergo Beckmann rearrangement to give formanisidide, both isomers giving solely anisonitrile or anisamide.[18b,21]

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Since the low material balance reported for the Schmidt reaction on anisaldehyde at the higher ratio of sulfuric acid raises the question of whether a considerable amount of formanisidide may not after all have been formed, and either lost by sulfonation or condensation with anisaldehyde, or diverted to tetrazole, we re-examined this experiment. We are able to confirm the qualitative result of McEwen, *et al.* that anisonitrile or its hydrolysis products are the major products, and to state that the formation of tetrazoles is real, although small. We isolated less than 1 per cent of anisidine (presumably derived from formanisidide), while the sum of anisonitrile and products from it amounted to ca. 72 per cent. Among these was 4·7 per cent of a basic solid, apparently identical with the N-anisoylanisamidine reported by Francis and Davis.[25] Examination of the aqueous mother liquor for non-extractable organic substances showed the presence of much diazotizable amine, presumably in the form of a sulfonic acid. Sequestering of formanisidide by sulfonation is not surprising in view of the fact that its ring is the most reactive of all those in the systems studied in the Schmidt reaction. Furthermore, experiments with formanisidide and anisaldehyde in simulated Schmidt reaction conditions showed that formanisidide does not survive, but undergoes conversion to anisaldehyde *p*-methoxyanil and then to sulfonation and hydrolysis products. We were also able to isolate 1·4 per cent of 1-*p*-anisyl-5-aminotetrazole (which could as well have arisen by a secondary reaction on anisonitrile as from initial migration of the anisyl group). While we were not able to assess quantitatively the production of substances derived from aryl migration, we can say that the Schmidt reaction on anisaldehyde should no longer be regarded as anomalous.

In summary, we can say that the mechanism for the Schmidt reaction on ketones proposed in 1948 can, when considered with insight, account for the many apparently anomalous phenomena that have been encountered since then, and that geometrical isomerism lies at the root of the causes of the observed ratios of amide isomers. The simplified interpretation in the form of the rule that that group migrates preferentially which has the greatest bulk in the neighborhood of the carbonyl group may have drastic exceptions where either conjugation or chelation come into play, and may owe its reliability in saturated aliphatic systems to the fact that migration aptitudes have their influence in the same direction.

[24] W. Swietoslawski and M. Popow, *Bull. Soc. Chim. Fr.* [4], **35**, 137 (1924).
[25] F. E. Francis and O. C. M. Davis, *J. Chem. Soc.* **85**, 1535 (1904).

## EXPERIMENTAL*

*Preparation of ketones.* *o*-Methylbenzophenone, b.p. 128–130°/1·5 mm (reported[26] 134–137°/2 mm) was prepared from *o*-tolunitrile and phenylmagnesium bromide. *o*-Ethylbenzophenone, b.p. 108–111°/0·3 mm (reported[27] 165°/18 mm) was prepared from *o*-ethylbenzonitrile, b.p. 79·5°/4·5 mm. $n_D^{20}$ 1·5229, $d_4^{25}$ 0·9715 (reported[28] b.p. 103°/19 mm, $n_D^{20}$1·5232), and phenylmagnesium bromide, *o-Ethylbenzophenone* 2,4-*dinitrophenylhydrazone*, prepared in the conventional manner, melted over a wide range even when freed from reactants.† Incomplete dissolution of this product in boiling alcohol left an undissolved portion which, after recrystallization from alcohol and ethyl acetate, gave orange needles, m.p. 174–178·5°. (Found: C, 64·44; H, 4·69; N, 14·02. $C_{21}H_{18}N_4O_4$ requires: C, 64·60; H, 4.65; N, 14·35%).

1-Benzoylnaphthalene, m.p. 75–76° (reported[29] 75·5–76°) was prepared from α-naphthylmagnesium bromide and benzonitrile and recrystallized from alcohol.

*o-Isopropylbenzonitrile and o-isopropylbenzamide.* The mixture of products from the mononitration[40] of cumene at 25° was fractionated twice through a three-foot spinning-band column under reduced pressure, and a center cut of *o*-nitrocumene of constant boiling point, 112°/13 mm, and refractive index, $n_D^{20}$ 1·5248, was obtained (reported b.p. 115°/13 mm,[41] $n_D^{20}$ 1·5248,[41] 1·52420,[40] 1·5259[42]). *o*-Nitrocumene was reduced in 90% yield with powdered iron and hydrochloric acid according to the method of Haun and Kobe[40] for mixed nitrocumenes, but using longer reaction time. The amine hydrochloride was recrystallized from benzene before further use and was converted in part to the free amine, b.p. 102·5–103·5°/12·5 mm, $n_D^{25}$ 1·5472, $d_4^{25}$ 0.9614 (reported[43] b.p. 102°/14 mm, $n_D^{25}$ 1·5494).

A diazotized solution of 25·7 g *o*-isopropylaniline hydrochloride was neutralized and combined with a solution of cuprous cyanide.[44] The addition was made as rapidly as possible in order to avoid excessive decomposition of the diazonium salt, and the mixture was kept at −3–0° all the time. The stirred mixture was allowed to warm to room temp and finally heated on the steam bath until evolution of nitrogen ceased. It was distilled with super-heated steam and ca. 2 l. of distillate was collected. Distillation of the benzene extracts of the steam distillate afforded 12·8 g (59%) *o*-isopropylbenzonitrile, b.p. 101–104°/15 mm. A small portion was redistilled for analysis, b.p. 106°/16 mm, $n_D^{20.5}$ 1·5144 (Found: C, 82·79; H, 7·55; N, 9·52. $C_{10}H_{11}N$ requires: C, 82·72; H, 7·64; N, 9·65%.

*o*-Isopropylbenzonitrile (8·2 g) was converted by 30% hydrogen peroxide and alcoholic base to *o-isopropylbenzamide* (4 g, 67% based on recovered nitrile), white needles, m.p. 123–123·5°, from petroleum ether (b.p. 90–100°) (Found: C, 73·73; H, 8·02; N, 8·59. $C_{10}H_{13}NO$ requires: C, 73·59; H, 8·03; N, 8·58%).

*o-Isopropylbenzophenone.* To a solution of the Grignard reagent from 12·1 g bromobenzene in 80 ml ether, prepared under nitrogen, a solution of 9·2 g *o*-isopropylbenzonitrile in 10 ml ether was added dropwise (3–4 min) at room temp. The mixture was heated under reflux for 1·5 hr and allowed to stand over-night at room temp. It was poured on ice, acidified with 50% $H_2SO_4$ and heated on the steam bath for 24 hr after the ether was removed. The organic layer was taken up in benzene and washed with dil sodium carbonate. Distillation at 0·6 mm gave 10·9 g (77%) of *o*-isopropylbenzophenone, collected in two fractions: (a) b.p. 121–123° (1·7 g) and (b) b.p. 123·5-124° (9·2 g). A sample from the latter was used for analysis (Found: C, 85·47; H, 6·95. $C_{16}H_{16}O$ requires: C, 85·68; H, 7·19%).

* Melting points are uncorrected and analyses are by Spang Microanalytical Laboratory and by Mrs. A. Griffin and Mr. G. Kodama of the Department of Chemistry, University of Michigan.

† It is quite reasonable to expect two stereoisomeric 2, 4-dinitrophenylhydrazones from *o*-substituted benzophenones; cf. similar derivatization of *m*-chlorophenyl α-naphthyl ketone by R. S. Cahn, W. O. Jone and J. L. Simonsen, *J. Chem. Soc.* 444 (1933). Separation of their mixtures may, however, be considerably difficult. We have not been able to improve the melting range 184–190°, reported by M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.* **63**, 1517 (1941), for *o*-methylbenzophenone 2,4-dinitrophenylhydrazone. Likewise, from *o*-ethylbenzophenone only one isomer was obtained relatively pure.

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[43] C. Hansch and G. Helmkamp, *J. Amer. Chem. Soc.* **73**, 3080 (1951).
[44] H. T. Clarke and R. R. Read, *Organic Syntheses* (2nd Ed.) Coll. Vol. I, p. 514. John Wiley, New York (1941).

o-*Isopropylbenzophenone* 2,4-*dinitrophenylhydrazones* were prepared from fraction (a) of *o*-isopropylbenzophenone. Approximately half of the crude product was dissolved in a limited amount of boiling alcohol containing a little ethyl acetate. The undissolved portion was then recrystallized twice from alcohol and ethyl acetate, giving scarlet needles, m.p. 204–206·8° (Found: C, 65·32; H, 4·80; N, 13·67. $C_{23}H_{20}N_4O_4$ requires: C, 65·33; H, 4·99; N, 13·86%).

The portion of the product which dissolved in alcohol was recovered and again treated with an insufficient amount of boiling solvent. This time, however, the soluble portion of the partially dissolved material was retained. Repetition of this process finally afforded a minute amount of orange needles, m.p. 142–143° (Found: C, 65·46; H, 4·78; N, 14·18. $C_{22}H_{20}N_4O_4$ requires: C, 65·33; H, 4·99; N, 13·86%).

It is not certain whether this lower melting 2,4-dinitrophenylhydrazone is a structural or geometrical isomer of the main product.

*o-Bromo-t.-butylbenzene*. Twelve grams of 2-bromo-4-nitro-t.-butylbenzene[45] was reduced in a Parr hydrogenator in the presence of 0·1 g Adams catalyst 80 ml alcohol and 10 ml conc HCl. The yield of 2-bromo-4-amino-t.-butylbenzene hydrochloride[45] was quantitative; it was deaminated to *o*-bromo-t.-butylbenzene, $n_D^{20}$ 1·5438, as described by Crawford and Stewart.[45]

In another instance, when a neutral alcoholic medium and a higher ratio of nitro-compound to catalyst were employed (19·5 g–0·1 g), products resulting from incomplete reduction were also isolated. They precipitated from the reaction mixture as an orange solid (1 g), which was separated by chromatography on alumina with pet ether (b.p. 30–60°) as solvent into two compounds: *3,3′-Dibromo-4,4′-di-t.-butylazobenzene*, orange, m.p. 170–172° was eluted first (Found: C, 53·28 H, 5·36. $C_{20}H_{24}Br_2N_2$ requires: C, 53·13; H, 5·35%).

*3,3′-dibromo-4.4′-di-t.-butylazoxybenzene*, yellow, m.p. 135–136°, was eluted last. (Found: C, 51·50; H, 5·10; N, 5·98. $C_{20}H_{24}Br_2N_2O$ requires: C, 51·53; H, 5·17; N, 5·98%).

*o-t.-Butylbenzophenone*, o-*t.-butylbenzophenone imine and hydrochloride*. To a solution of the Grignard reagent from 8 g *o*-bromo-t.-butylbenzene in 40 ml ether was added at room temp 10·6 g freshly distilled benzoyl chloride in 10 ml ether, causing vigorous ebullition and instantaneous precipitation of salts. The mixture was refluxed for 6 hr, then poured in iced water. The organic layer was shaken several times with 25% NaOH until removal of benzoyl chloride by hydrolysis was complete. Distillation gave a forerun of t.-butylbenzene (27%) and 5·9 g (66%) *o*-t.-butylbenzophenone, b.p. 124·5–125°/0·4 mm, which gradually solidified and, after recrystallization from aqueous methanol, melted at 71–72°. (Found: C, 85·84; H, 7·66. $C_{17}H_{18}O$ requires: C, 85·67; H, 7·61%).

The addition of 4·2 g benzonitrile to the Grignard reagent from 8·7 g *o*-bromo-t.-butylbenzene gave *o*-t.-butylbenzophenone imine, which was isolated as the hydrochloride (4·6 g, 42%), m.p. 248–250° after recrystallization from alcohol. (Found: C, 74·56; H, 7·45; N· 5.36. $C_{17}H_{20}ClN$ requires: C, 74·57; H, 7·36; N, 5·12%). The free imine, after repeated recrystallizations from light pet ether, m.p. 58–59·5°. (Found: N, 5·84. $C_{17}H_{19}N$ requires: N, 5·90%).

The imine was not appreciably hydrolyzed to the ketone by refluxing in conc hydrochloric acid overnight. Likewise it was recovered unchanged in 95% yield after boiling in aqueous alcoholic potassium hydroxide for 8 days.

*o-t.-Butylaniline*. *o*-Nitro-t.-butylbenzene (13·5 g), prepared in 76% yield by the deamination[46,*] of 2-nitro-4-amino-t.-butylbenzene,[47] was reduced with hydrogen and Adams catalyst to *o*-t.-butylaniline (8·5 g, 76%), b.p. 112·5°/6 mm, $d_4^{25}$ 0·9576, $n_D^{20}$ 1·5455 (reported[48] b.p. 106·5°/10 mm $n_D^{20}$ 1·5453), after isolation via the hydrochloride and distillation through a one-foot spinning band column at 13 mm.

*Preparation of amides*. The amides used in the preparation of calibration mixtures for the infrared

* Both procedures given in ref. 45 were used. Procedure I, which employs hypophosphorous acid as the source of the requisite acidity in the diazotization step, gave lower yields plus 17% of buff colored 1,3-bis-(3-*nitro*-4-*t.-butylphenyl*) *triazene*, m.p. 187–189°. (Found: C, 60·13; H, 6·15. $C_{20}H_{25}N_5O_4$ requires: C, 60·13; H, 6·31%).

The triazene was not isolated when hydrochloric acid (Procedure II), a stronger acidic medium, was used during diazotization.

[45] M. Crawford and F. H. C. Stewart, *J. Chem. Soc.* 4443 (1952).
[46] N. Kornblum and D. C. Iffland, *J. Amer. Chem. Soc.* **71**, 2137 (1949).
[47] J. B. Shoesmith and A. Mackie, *J. Chem. Soc.* 2336 (1928).
[48] H. C. Brown and K. L. Nelson, *J. Amer. Chem. Soc.* **75**, 27 (1953).

analysis were synthesized by standard methods from the corresponding acid chlorides and amines, unless otherwise indicated: *o*-toluanilide, m.p. 125–126° (reported[49] 129–129·5°); benzo-*o*-toluidide, m.p. 142·5–143° (reported[49] 142–143°); *o*-ethylbenzanilide, m.p. 141–142·5°; benzo-*o*-ethylanilide, m.p. 152·5–153° (reported[50] m.p. 146°). (Found: C, 79·88; H, 6·77; N, 6·16. Calc. for $C_{16}H_{15}NO$: C, 79·97; H, 6·71; N, 6·22%); benzo-*o*-isopropylanilide, m.p. 147–147·5° (reported[51] m.p. 149°); benzo-*o*-t.-butylanilide, m.p. 194–194·8° (reported[51] m.p. 196°) (also exists in another modification, m.p. 190–190·5°); α-naphthanilide, m.p. 161–162·5° (reported[52] m.p. 160–161°); 1-benzamidonaphthalene, m.p. 159–161° (reported[53] m.p. 159–160°).

*o*-Isopropylbenzanilide, prepared from *o*-isopropylbenzoic acid obtained by the method of Sudborough,[54] had m.p. 135·5–136·5°. (Found: C, 80·16; H, 7·07; N, 5·88. $C_{16}H_{17}NO$ requires: C, 80·30; H, 7·16; N, 5·85%).

*o-t.-Butylbenzanilide*, m.p. 178·5–180·5°, was prepared from *o*-t.-butylphenylmagnesium bromide and phenyl isocyanate. (Found: C, 80·35; H, 7·47; N, 5·50. $C_{17}H_{19}NO$ requires: C, 80·57; H, 7·56; N, 5·53%).

*Schmidt reactions.* The procedure used, unless otherwise stated, was to add 1·0 g solid sodium azide portionwise to a solution of 0·01 mole ketone and 0·028 mole conc sulphuric acid in 25 g fused trichloroacetic acid at 60 ± 2°. The addition was customarily made over 3–9 hr, and the reaction was allowed to continue for several hours until visible gas evolution had ceased. The products precipitated when the mixture was diluted with water and neutralized with ammonia or dil alkali. The mixture of amides was collected by filtration, washed with water, and freed of unreacted ketone either by steam distillation or by washing with a few ml cold light pet ether. When the nitrogen analysis of the mixture was in good agreement with the calculated value for the amides the mixture was used in the spectrophotometric determination of isomer ratios without further purification.

With an addition time of 2·75 hr, 1·96 g *o*-methylbenzophenone gave 1·70 g amides (Found: N, 6·62. Calc. for $C_{14}H_{13}ON$: N, 6·63%), and 0·26 g of yellow oil (pet ether wash) presumed to be unreacted ketone. With an addition time of 9 hr, the yield of amides was 2·11 g (Found: N, 6·65%).

*o*-Ethylbenzophenone (2·10 g) with an addition time of 4·5 hr gave 1·81 g amides (Found: N, 6·28. Calc. for $C_{15}H_{15}ON$: N, 6·22%) and 0·33 g unreacted ketone (pet ether wash). With an addition time of 6 hr the yield of amides was 2·15 g, after purification by steam distillation (Found: N, 6·25%). The distillation removed only 0·03 g of a mixture of amides and ketone, which was not considered further.

From 2·24 g *o*-isopropylbenzophenone with 9·5 hr addition time 2·30 g amides was obtained, after purification by steam distillation (Found: N, 5·88. Calc. for $C_{16}H_{17}ON$: N, 5·85%). With an addition time of 7 hr and the same method of purification, another sample of *o*-isopropylbenzophenone gave 2·23 g amides (Found: N, 6·05%), and 0·07 g of a mixture of amides and ketone.

The Schmidt reaction of *o*-t.-butylbenzophenone was performed as follows. Sodium azide (3·4 g) was added in small portions during 76 hr to a solution of 3·4 g of the ketone (m.p. 70·5–72°; chromatographed in pet ether over alumina) and 12 g conc sulphuric acid in 100 g trichloroacetic acid. After standing for 12 hr the mixture was poured in iced water and basified. The precipitated solid was filtered, washed free of base and dried. It was combined with the evaporated ether extracts of the aqueous phase, dissolved in ca. 50 ml benzene and chromatographed over alumina (300 g). Unreacted ketone (9·17 g, m.p. 68–70·5°) was eluted first with benzene. After a clean break, during which the solvent was gradually changed to chloroform and then to absolute alcohol, an "amide fraction" was eluted with the latter, weighing 0·237 g and consisting of brown semi-solid material. By recrystallization from a mixture of benzene and pet ether, 0·063 g of almost white solid was obtained. The unreclaimed material (0·173 g) was chromatographed again in the same manner. The first fraction (0·01 g) contained oily material soluble in pet ether and was discarded. It was followed by fractions containing a white solid and, later, oil which could be induced to crystallize by treating with benzene and pet ether and seeding. The combined yield of all crystalline material from the "amide fraction" was thus raised to 0·118 g (Found: N, 6·01, 6·03. Calc. for $C_{17}H_{19}NO$: N, 5·53%). It is possible that it was contaminated with some *sym*-phenyl-*o*-t-butylphenylurea

[49] A. Brückner, *Liebig's Ann.* **205**, 130 (1880).
[50] J. von Braun, O. Bayer and G. Blessing, *Ber. Dtsch. Chem. Ges.* **57**, 392 (1924).
[51] P. Grammaticakis, *Bull. Soc. Chim.* 134 (1949).
[52] M. Betti and A. Beccioloni, *Gazz. Chim. Ital.* **45**(II), 224 (1915).
[53] J. Loevenich and A. Loeser, *Ber. Dtsch. Chem. Ges.* **60**, 322 (1927).
[54] J. J. Sudborough, *J. Chem. Soc.* **67**, 602 (1895).

(Calc. for $C_{17}H_{20}N_2$: N, 10·5%). The infrared spectrum of the product disclosed ca. 20% of contamination. The isomer ratio obtained thereby should be considered only as a very rough estimate.

1-Benzoylnaphthalene (2·32 g) with an addition time of 8 hr gave 2·42 g amides (washed with pet ether b.p. 90–100°) (Found: N, 5·67. Calc. for $C_{17}H_{19}NO$: N, 5·66%).

*Oximations and Beckman rearrangements.* The oximations at 118° were performed by maintaining at a gentle reflux a solution of 0·01 mole ketone and 1·0 g hydroxylamine hydrochloride in 10 ml pyridine (the temperature of the refluxing liquid was 118 ± 2°). After pouring in water, crystallization of the oily oximes was facilitated by acidifying with dil hydrochloric acid and was usually complete in two to 3 hr. The solid oximes were filtered, washed with water and dried. They were rearranged at room temp in benzene solution by the addition of 3 g phosphorus pentachloride in 3 portions during ½ hr. After 3–8 hr, the mixture was decomposed with water, the benzene was evaporated and the crystalline amides were filtered and washed with water. Occasionally they were washed with 1N NaOH to remove unreacted oximes, but a significant amount was never found. After drying, the amides were washed with light pet ether to remove unreacted ketone.

Oximation of 1·96 g *o*-methylbenzophenone gave 2·03 g (96%) of oxime which afforded upon rearrangement 1·99 g amides (Found: N, 6·62. Calc. for $C_{14}H_{13}ON$: N, 6·63%).

From 2·10 g *o*-ethylbenzophenone 2·18 g (97%) of oximes was obtained, giving 2·11 g amides upon rearrangement (Found: N, 6·18. Calc. for $C_{15}H_{15}ON$: N, 6·22%).

Oximation of 2·24 g *o*-isopropylbenzophenone gave 2·32 g (97%) oximes, which was converted to 2·29 g amides (Found: N, 5·89. Calc. for $C_{16}H_{17}ON$: N, 5·85%).

The oximes from 1-benzoylnaphthalene (2·32 g) did not completely crystallize after standing for 8 hr in the refrigerator, but did so when kept an additional 3 hr at room temp. The yield of amides was 2·05 g (Found: N, 5·41. Calc. for $C_{17}H_{13}ON$: N, 5·66%).

The oximations at 60° were performed in a similar manner, using an oil bath at 60 ± 2, and were allowed to proceed for 12 days. In anticipation that the presence of unreacted ketone might render difficult the crystallization of the oximes, the reaction mixtures were decomposed with water and then extracted with benzene. The extracts were washed with 10% HCl, then with a solution of sodium chloride until free of acid, and dried over magnesium sulphate. The Beckman rearrangement was performed without isolation of the oximes. The resulting amides were treated as above.

In this manner 1·97 g *o*-methylbenzophenone gave 1·97 g amides (Found: N, 6·54%). *o*-Ethylbenzophenone (2·10 g) gave 2·08 g amides (Found: N, 6·24%). *o*-Isopropylbenzophenone (2·05 g) gave 1·64 g amides (Found: N, 5·82%) and 0·42 g ketone, left as an amber oil upon evaporation of the pet ether wash.

*Determination of isomer ratios.* The ratios of isomeric amides were determined by infrared analysis, using 5% (*w/v*) solutions in chloroform, matched 0·1 mm sodium chloride cells and a Perkin–Elmer Model 21 Infrared Spectrophotometer. Calibration mixtures were prepared from pure samples of the amides and measurements were made at several selected frequencies. *A priori* weights were assigned to the measurements at each frequency based on the rate of change of the transmittance with composition and the reproducibility of the transmittance readings. The value of the ratio was taken as the average of the values obtained at various frequencies. In general the weighted averages differed less than one percent unit from the unweighted. The following frequencies were used for the products of each ketone: *o*-Methylbenzophenone: 1602, 1473, *1478*, 1443, 1317 and 702 $cm^{-1}$. *o*-Ethylbenzophenone: 1595, 1463, *1452* and 1315 $cm^{-1}$. *o*-Isopropylbenzophenone: 1594, 1580, *1466–8*, 1450, 1314 and 700 $cm^{-1}$. *o*-t-Butylbenzophenone: 1602, 1580, 1475 and 1315 $cm^{-1}$. 1-Benzoylnaphthalene: 1596, *1485*, 1460, 1438, 1344, 1313 and 700 $cm^{-1}$. The italicized frequency was the most sensitive.

*Schmidt reaction on anisaldehyde.* To 23·4 g sodium azide overlaid with 225 ml "reagent" grade benzene was added 55 ml conc. $H_2SO_4$ dropwise, while the temp was kept between 10 and 15°. The sulphuric acid was then followed by 20·4 g anisaldehyde (Eastman "White Label"), also added dropwise at 10–15°, and the mixture was stirred at room temp for 2 hr more, heated at ca. 45° for 1 hr, and then decomposed with ice. The resulting yellow-brown precipitate was filtered off and washed with benzene and water; wt. 17·02 g. This material was then swirled with 250 ml 2% NaOH solution at room temp; the dull yellow residue of crude anisamide weighed 14 g, m.p. 157–162°. Recrystallization from acetone gave successive crops of glassy crystals of anisamide, m.p. 167–168° (reported[55] m.p. 166·5–167·5°), total wt. 12·3 g.

[55] E. Bamberger and N. Pemsel, *Ber. Dtsch. Chem. Ges.* **36**, 371 (1903).

Concentration of the mother liquors and crystallization of the residue alternately from methanol and acetone gave 0·24 g of prisms, m.p. 231–233° with effervescence, an approximately equal quantity of the same material of lower purity, and 0·31 g (1·5%) of N-anisoylanisamidine, m.p. 156–158°, undepressed when mixed with a sample from another fraction of the reaction mixture (*vide* infra). (Owing to the closeness of their m.ps., anisamide, m.p. 166–1/2–167–1/2°, and anisoylanisamidine, m.p. 162–163°, cannot be distinguished with certainty when not highly purified, and the identities reported in the following description were therefore in all cases confirmed by mixed m.ps.).

The substance of m.p. 231–233° has the same empirical formula as anisamide, but its infrared spectrum (Nujol mull) differs from it as indicated: *Anisamide:* 3370, 3040–3160, 1685 shouldering on 1615, 1575, 1515, and 1460 $cm^{-1}$; *isomer*, m.p. 231–233°: 3170–3250, 1605 (plus weak, broad shoulder in 1650–1720 region), 1555, 1485, 1465 $cm^{-1}$, plus additional differences at lower frequencies. (Found: C, 63·56; H, 5·95; N, 9·34. $C_8H_9O_2N$ requires: C, 63·56; H, 6·00; N, 9·27). Hydrolysis of 0·11 g by heating for 4 days with 1:1 HCl gave 0·05 g anisic acid, m.p. 181–182 1/2° (reported[54] m.p. 183–184°). The filtrate was made strongly basic with potassium hydroxide, heated for 4 hr, cooled, and treated with 4 drops benzoyl chloride. No benz-*p*-anisidide, or any other isoluble substance, was produced. Acidification of the mixture gave an immediate precipitate. The mixture was diluted to ca. 20 ml, heated to near boiling, and filtered. The solid so obtained was crude anisic acid, wt. 0·03 g, m.p. 174–179° (180–182° when mixed with authentic anisic acid), total yield 72%. Recrystallization of this crop from carbon tetrachloride gave 0·015 g, m.p. 180 1/2–183°. (When the hydrolysis was carried out with hydrochloric acid only, treatment of the filtrate from the first crop of anisic acid with benzoyl chloride and sodium carbonate gave an impure, solid, neutral substance, m.p. 159–164°, which may have been crude dianisamide, reported m.p. 170°[55]). Although the analysis and hydrolysis of the substance of m.p. 231–233° corresponds to a hydrate of anisoylamisamidine, we were unable to achieve an interconversion with it.

The liquid portion of the original reaction mixture (benzene-water solution) was separated into its layers, and the aqueous phase was extracted with ether. The combined non-aqueous phases were washed with sodium hydroxide solution and with water; acidification of these washings precipitated 0·22 g (1%) anisic acid, m.p. 180–183°. The washed benzene–ether solution was then allowed to stand with sat sodium bisulphite solution overnight to detect unreacted anisaldehyde, but only 0·2 g bisulphite addition compound was formed. Evaporation of the filtered organic phase left a tan, crystalline residue, wt. 2·5 g. Extraction with warm ligroin–benzene mixture left 0·32 g anisamide (1·4%), m.p. 168–170°. The extracts were evaporated and crystallized from methanol, giving a few glassy crystals, m.p. 209–215°. Dilution of the methanolic filtrate with water gave anisonitrile in several crops, total wt. 1·34 g (7·3%), m.p. from 55–59° to 60–62°.

The aqueous sulphuric acid portion of the original reaction mixture was alkalized with a mixture of sodium and potassium hydroxides, which precipitated 0·86 g solid showing an indefinite m.p. Recrystallization from absolute alcohol (charcoal) gave N-anisoylanisamidine in two crops, total wt. 0·67 g (3·2%), m.p. 161–163° (Found: C, 67·63; H, 5·91; N, 9·74. Calc. for $C_{16}H_{16}O_2N_2$: C, 67·59; H, 5·67; N, 9·85). The infrared spectrum (Nujol mull) of a sample recrystallized from acetone showed absorptions at 3120–3200 (with a prominent shoulder at 3200–3300), 1605, 1565, and 1465 $cm^{-1}$. Hydrolysis of 0·11 g by heating with 10% HCl for several hours gave 0·115 g (98%) anisic acid, m.p. 184–185°, undepressed by mixture with an authentic sample.

The alkaline, aqueous solution from which the crude anisoylanisamidine had been filtered was extracted repeatedly with chloroform and ether. Treatment of the aqueous layer with benzoyl chloride gave only 0·18 g of a solid that did not melt below 250° and could not be purified, since it was insoluble in all ordinary solvents. Extraction of the combined chloroform–ether layers with dil HCl and treatment of the acid extract with benzoyl chloride and alkali gave 0·39 g crude solid, m.p. 143–150°, which gave 0·10 g (0·3%) benzanisidide, m.p. 158–160°, after recrystallization from alcohol. Evaporation of the acid-washed chloroform–ether solution gave 0·11 g (0·4%) anisamide, m.p. 164–167°.

In another experiment, conducted similarly with 10·4 g anisaldehyde, the diluted reaction mixture from which the precipitated anisamide had been filtered was separated from the benzene layer and freed of hydrogen azide by concentration in an air stream. The solution was then made basic with sodium hydroxide and filtered from a grey-brown, crystalline precipitate, wt. 0·2 g, m.p. 150–160°, and extracted with 6 portions benzene. Evaporation of the extracts left a small amount of crude, dark anisidine, m.p. 70–77°. A portion of the aqueous solution was then acidified, treated with

sodium nitrite and then with sulfamic acid, and coupled to alkaline $\beta$-naphthol; a deep red-purple dye was produced, which stayed in solution while it was alkaline, but was precipitated by acid.

The crystalline material of m.p. 150–160° was recrystallized from hot water and ethanol to obtain a pure sample, m.p. 201–202° dec (reported[56] for 1-*p*-anisyl-5-aminotetrazole, m.p. 209–210°), which reduced Tollens' reagent slowly when heated (Found: N, 36·29. Calc. for $C_8H_9N_5O$: N, 36·63%).

[56] W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.* **18**, 779 (1953).

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# BICYCLANES—II[1]

## ON THE PREPARATION AND HALOGENATION OF BICYCLO[2,2,2]OCTANE

A. F. BICKEL, J. KNOTNERUS, E. C. KOOYMAN* and G. C. VEGTER
Koninklijke/Shell-Laboratorium, Amsterdam
(Shell Internationale Research Maatschappij N.V.)

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**Abstract**—In the presence of traces of acidic materials, Diels–Alder condensation of ethylene and cyclohexadiene-1,3 gives, besides the expected bicyclo[2,2,2]octene-2, the isomeric bicyclo[3,2,1]octene-2; the latter is formed through acid-catalysed rearrangement. Its structure was proved among other things by stepwise oxidative degradation to cyclopentane-*cis*-1,3-dicarboxylic acid.

Competitive halogenations of bicyclo[2,2,2]octane and cyclohexane showed that the methylene groups in the latter are somewhat more reactive. Reactivity ratios decreased at increasing temperatures.

The reactivity of the bridgehead positions in bicyclo-octane towards hydrogen removal is appreciably larger than that of the methylene groups, in contrast to the situation in bicyclo[2,2,1]-heptane. This is probably due to the greater flexibility of the bicyclo-octane skeleton permitting a near-planar configuration at the bridgehead. Some of the differences between the bicyclo[2,2,2]octane, bicyclo[2,2,1]heptane and cyclohexane systems are briefly discussed.

IN Part I two of us[1] described the halogenation of bicyclo[2,2,1]heptane, using various free-radical methods. In continuation of this work the preparation and properties of bicyclo[2,2,2]octane were examined.

Model considerations suggest that this bicyclane has a rigid structure, while its bond angles are probably close to the tetrahedral values. It seemed of interest, therefore, to compare its properties with those of the also rigid but highly strained bicycloheptane.

Bicyclo[2,2,2]octane was synthesized by Alder and Stein, who started from cyclohexadiene-1,3 and acrolein;[2] the corresponding bicyclene was also first prepared by indirect methods, starting from cyclohexadiene-1,3 and ethyl acrylate.[3]

Walborsky and Loncrini were the first to report the direct synthesis of bicyclo-[2,2,2]octene-2 from cyclohexadiene-1,3 and ethylene;[4] the same reaction was reported independently by Hine *et al.*[5]

The chemical behaviour of bicyclo[2,2,2]octane does not seem to have been studied so far; several derivatives have been prepared by indirect methods, however, e.g. the 1- and 2-halides.[6–9]

* Present address: Laboratory of Organic Chemistry, The University, Leiden.

[1] Bicyclanes–I: E. C. Kooyman and G. C. Vegter, *Tetrahedron* **4**, 382 (1958). In the present article the nomenclature has been changed to conform with the I.U.P.A.C. rules.
[2] K. Alder and G. Stein, *Liebigs Ann.* **514**, 1 (1934).
[3] R. Scha and O. Tramposch, *Ber. Dtsch. Chem. Ges.* **75**, 1379 (1942).
[4] H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.* **76**, 5396 (1954).
[5] J. Hine, J. A. Brown, L. H. Zalhow, W. E. Gardner and M. Hine, *J. Amer. Chem. Soc.* **77**, 594 (1955).
[6] G. Komppa, T. Hirn, W. Rohrmann and S. Beckmann, *Liebigs Ann.* **521**, 242 (1936).
[7] W. von E. Doering and M. Farber, *J. Amer. Chem. Soc.* **71**, 1514 (1949).
[8] H. M. Walborsky, *Experientia* **9**, 209 (1953).
[9] Adnan Abdul-Rida Sayigh, Columbia University, New York City, Diss. 1952.

The present paper mainly deals with the preparation and halogenation of bicyclo-[2,2,2]octane, starting from the above direct synthesis of the bicyclene; in this reaction, an isomer appeared to be formed under acidic conditions, viz. bicyclo-[3,2,1]octene-2.

1. *Diels–Alder condensation of cyclohexadiene*-1,3 *and ethylene*

Bicyclo[2,2,2]octene-2, m.p. 112–113°, b.p. 134°, was prepared in a glass-lined autoclave according to Hine *et al.*[5] When an unlined steel autoclave was used, however, a different olefin having the same boiling point but melting at 43–45° was obtained as the main product; catalytic hydrogenation of this material yielded a bicyclooctane melting at 136–137·5° (the melting point of bicyclo[2,2,2]octane is 174°). Literature data on the melting points of bicyclo[3,2,1]octene and -octane suggested that the compounds prepared in the steel autoclave were the [3,2,1]-isomers. Conclusive evidence to this effect is presented in §2.

Bicyclo[3,2,1]octene has also been mentioned by von Braun and Reitz[10] but these authors probably obtained it in admixture with bicyclo[3,3,0]octene, since hydrogenation produced a liquid; pure bicyclo[3,2,1]octane melts at 141° (cf. Birch *et al.*[11]).

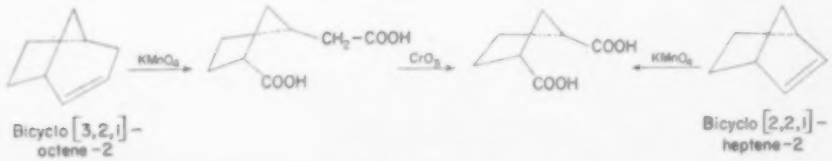
The above difference could be attributed to acid-catalysed isomerization of the normal Diels–Alder condensation product, since the addition of a small amount of pyridine led to the pure [2,2,2]-isomer even when an unlined steel autoclave was used. Moreover, the latter olefin could be rearranged to the [3,2,1]-isomer when heated to the reaction temperature of the Diels–Alder addition (250°) in the presence of moist ferric chloride in a glass-lined vessel; it appeared to be stable at this temperature in the absence of the catalyst.

Probably, our cyclohexadiene contained traces of organic bromides (e.g. bromocyclohexene) formed from the starting material dibromocyclohexane; these in turn produced some ferric bromide in the unlined steel vessel.

2. *Proof of structure of bicyclo*[3,2,1]*octene*-2 *by oxidative degradation*

Alder *et al.*, who prepared bicyclo[3,2,1]octene-2 along different routes, established its structure by ozonolysis.[12] We employed the following method:

Oxidation with potassium permanganate yielded a dicarboxylic acid $C_8H_{12}O_4$, which had been also obtained by Alder *et al.* upon ozonolysis of bicyclo[3,2,1]octene[12] as well as by oxidation of bicyclo[3,2,1]octanol-2.[13] Further oxidation of this acid by means of chromic acid in glacial acetic acid produced cyclopentane-*cis*-1,3-dicarboxylic acid, identical with a reference sample prepared by permanganate oxidation of bicyclo[2,2,1]heptene-2:




[10] J. von Braun and J. Reitz, *Ber. Dtsch. Chem. Ges.* **74**, 273 (1941).
[11] S. F. Birch, R. A. Dean, N. J. Hunter and E. V. Whitehead, *J. Org. Chem.* **22**, 1590 (1957).
[12] K. Alder, H. Krieger and H. Weiss, *Chem. Ber.* **88**, 144 (1955).
[13] K. Alder and E. Windemuth, *Ber. Dtsch. Chem. Ges.* **71**, 2404 (1938).

Oxidation of bicyclo[2,2,2]octene-2 is reported[4] to yield cyclohexane-*cis*-1,4-dicarboxylic acid besides other products.

On hydration with 60 per cent sulphuric acid, bicyclo[3,2,1]octene gave the known bicyclo[3,2,1]octanol-2, which was also obtained by Newman and Tien Yu on hydration of bicyclo[2,2,2]octene-2.[14]

3. *Chlorination of bicyclo*[2,2,2]*octane*

Chlorination reactions were carried out in carbon tetrachloride solution at 30°, using molecular chlorine as the reagent and light as the initiating agent. Conversions were about 30 per cent.

Chlorination products could not be readily separated from the parent hydrocarbon by fractional distillation. Reaction mixtures were therefore analyzed by infrared and mass spectrometry after removal of the solvent. Spectroscopic standards used for both methods consisted of pure samples of (a) bicyclo[2,2,2]octane, (b) 2-chlorobicyclo[2,2,2]octane, prepared by addition of HCl to the corresponding bicyclene,[4,7,8] and (c) 1-chlorobicyclo[2,2,2]octane prepared via the 1-carboxylic acid according to Sayigh.[9]

Results are given in Table 1.

Thus in bicyclo-octane the two bridgehead positions are about equally reactive with regard to hydrogen abstraction as the six methylene groups, i.e. the tertiary hydrogens are about six times as reactive as those in secondary positions.

4. *Competitive halogenations of bicyclo*[2,2,2]*octane and cyclohexane*

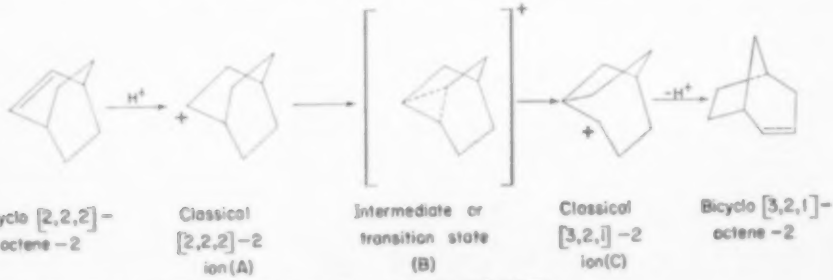
Equimolar amounts of the two hydrocarbons in carbon tetrachloride were reacted with molecular chlorine and bromine at 5° and at 80°. Conversions were about 10 per cent and ultra-violet light was the initiating agent. The products were analyzed by gas-liquid chromatography, which under our conditions failed to distinguish between the 1- and 2-halides of bicyclo-octane. Results are given in Table 2:

General trends appear to be similar for the two bicyclanes, relative reactivities being of the same order of magnitude and decreasing with increasing temperature.

## DISCUSSION

1. *Isomerization of bicyclo*[2,2,2] *to* [3,2,1]*octene-2 and related reactions*

According to Walborsky[8] these rearrangements should proceed through an intermediate or transition state of the non-classical ion type (B), formation of which is preceded and/or followed by that of a classical ion (A, C). In terms of this concept, the isomerization of bicyclo[2,2,2]octene-2 may be described as follows:




[14] M. S. Newman and Y. Tien Yu, *J. Amer. Chem. Soc.* **74**, 507 (1952).

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TABLE 1. CHLORINATION OF BICYCLO[2,2,2]OCTANE

| Products | Analysis* | |
|---|---|---|
| | Infra-red | Mass spectrometry |
| Bicyclo[2,2,2]octane | 74% ± 5% | ~70% |
| 1-Chlorobicyclo[2,2,2]octane | 16% ± 5% | ~24% |
| 2-Chlorobicyclo[2,2,2]octane | 14% ± 5% | |
| Trichloro compounds | | 2–5% |

* Mean values from several runs.

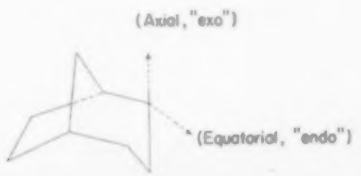
TABLE 2. COMPETITIVE HALOGENATIONS OF BICYCLO[2,2,2]OCTANE AND CYCLOHEXANE COMPARED WITH THOSE OF BICYCLO[2,2,1]HEPTANE AND CYCLOHEXANE

| Halogenating agent | Temperature | Relative reactivities | |
|---|---|---|---|
| | | $\frac{K_b(\text{icyclo-octane})}{K_c(\text{yclohexane})}$ (a) | $\frac{K_b(\text{icycloheptane})}{K_c(\text{yclohexane})}$ (b) |
| $Cl_2$ | 5° | 0·96 ± 0·05 | 0·99 |
| $Cl_2$ | 80° | 0·69 ± 0·03 | 0·79 |
| $Br_2$ | 5° | 3·1 ± 0·6 | 1·02 |
| $Br_2$ | 80° | 1·6 ± 0·2 | 0·55 |

(a) $K_b/K_c = \frac{\log (1 - (R_bCl)/(R_bH)_o)}{\log (1 - (R_cCl)/(R_cH)_o)}$, where $(R_bH)_o$ and $(R_cH)_o$ are the initial concentrations of the two hydrocarbons and $(R_bCl)$ and $(R_cCl)$ the final concentrations of the monohalides. Data given are mean values from at least four runs.
(b) cf. Part I.[1]

Other examples of the rearrangement A → C are the isomerization of the bromide under the influence of silver bromide[7] and the acid-catalysed hydration of bicyclo-[2,2,2]octene-2[14] to give the same carbinol as the [3,2,1]bicyclene, viz. the type C alcohol.

Since these reactions are probably reversible, product compositions should be controlled by thermodynamics. In the derivatives of type A, substituents are necessarily in the crowded axial position; in the type C compounds, the six-membered ring has the chair conformation, which permits a substituent to occupy a favourable equatorial position (D):




Axial and equatorial directions in a 2-substituted bicyclo [3,2,1] octane (D)

Similarly, formation of the [3,2,1]bicyclene from the [2,2,2]-isomer should be due to the relieving of strain involved in the formation of a cyclohexene ring having the "half-chair" rather than the "half-boat" conformation; here, too, the equilibrium lies far towards the side of the [3,2,1]-isomer.

So far, no definite experimental data appear to be available as regards the geometry of the 2-substituted bicyclo[3,2,1]octanes. According to the above reasoning, the substituents should be in the equatorial positions, i.e. away from the methylene bridge.* It may be noted, however, that the solvolysis of bicyclo[2,2,1]heptyl-2 halides or esters leads exclusively to exo-products.[15,16] This is what would be expected for a kinetically controlled process through B, which should produce the exo or axial C derivative, although this position is less favourable thermodynamically.

In various other instances, however, the skeletal rearrangement A → C does not occur.[8] Thus, the brosylate of A on solvolysis yields the carbinol of A; addition of HCl to bicyclo[2,2,2]octene-2 leads to the chloride of A. Further, 2-aminobicyclo-[2,2,2]octane and nitrous acid give the non-rearranged carbinol. As in the case of bicyclo[2,2,1]heptene-2, free-radical additions at the double bond in bicyclo[2,2,2]-octene-2 give non-rearranged products. Halogenation of bicyclo[2,2,1]heptane[1] as well as of bicyclo[2,2,2]octane also produces type A products.

On the basis of many of the above data, Walborsky supposed that the ion A would rearrange only when its lifetime was sufficiently long,[8] step A → B being relatively slow.

Doubt as regards this plausible hypothesis arises from the fact that the opposite rearrangement has been observed, bicyclo[3,2,1]octene-2 reacting with acetic acid containing some sulphuric acid to produce mainly the acetate of A.[12] In our opinion this means that B reacts preferentially and irreversibly with acetate ion or acetic acid in such a fashion that the thermodynamically unfavourable [2,2,2]-acetate is formed. Therefore, failure to rearrange in reactions of type A derivatives may be due at least in part to kinetic control involving a reaction of the intermediate B and need not be attributable exclusively to the slowness of the step A → B as assumed by Walborsky. Apparently, this point requires further experimentation.

## 2. *Halogenations of bicyclo[2,2,2]octane*

The higher reactivity of tertiary hydrogens compared with secondary ones contrasts with the very low reactivity of the bridgehead positions in bicyclo[2,2,1]heptane. Apparently, the bicyclo-octane molecule is sufficiently flexible to permit the near-planar configuration at the bridgehead required for a favourable transition state. The bridgehead bromide, however, is reported to be about $10^5\times$ less reactive in solvolysis than t-butylbromide, though much more reactive than 1-bromobicyclo-[2,2,1]heptane.[17] This would indicate that the transition state in a solvolysis reaction has a greater sensitivity as regards deviations from "planarity" than that in a hydrogen abstraction by atomic chlorine. In the latter reactions only little bond-breaking may

* In a paper on "*cis*- and *trans*-bicyclo[3,2,1]octanol-2" by A. A. Youssef, M. E. Baum and H. M. Walborsky, the preference for the equatorial form of the alcohol is demonstrated experimentally, the equatorial/axial ratio being about 1g at equilibrium.

[15] J. D. Roberts, W. Bennett and R. Armstrong, *J. Amer. Chem. Soc.* **72**, 3329 (1950).
[16] S. Winstein and D. Trifan, *J. Amer. Chem. Soc.* **74**, 1147 (1952).
[17] W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher and W. P. Whelan, Jr., *J. Amer. Chem. Soc.* **75**, 1008 (1953).

be necessary to reach the transition state and this would then be subject to little strain at the bridgehead.[18]

As pointed out in Part I,[1] the activation enthalpy for hydrogen removal from the methylene groups by a chlorine atom is probably lower in bicyclo[2,2,1]heptane than in cyclohexane (cf. Table 2). The same may be true in the case of bicyclo[2,2,2]octane; here, a numerical comparison cannot be made from the data because of the appreciable contributions from the tertiary hydrogens (Table 1). The lower overall reactivity of bicyclo[2,2,2]octane compared with cyclohexane (Table 2) is apparently due to a lower entropy factor, the reason for which is not obvious. It may be noted that the acetolysis rate of bicyclo[2,2,2]octyl-2-brosylate is appreciably greater than that of the cyclohexyl ester;[19] here, the strain should be relieved to a larger extent among other things since the brosylate group is more bulky than a hydrogen atom.

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## EXPERIMENTAL

### 1. *Preparation of bicyclo*[3,2,1]*octene-2 and bicyclo*[2,2,2]*octene-2*

A 2-litre steel autoclave, containing 103 g cyclohexadiene-1,3 prepared as described by Hine *et al.*[5] was charged with ethylene to a pressure of 50 atm. The reaction vessel was set in rotation and kept at 280° ± 20° for 34 hr. Distillation of the contents yielded 25 g of a liquid with b.p. 133–135°, $n_D^{20} = 1{\cdot}4793$; $d_{19}^{19} = 0{\cdot}8961$. This liquid was dissolved in 30 ml methanol and cooled to −60°. The crystals formed were recrystallized from pentane and finally sublimed, m.p. 43–45° (lit[12] 47°).

Ozone absorption indicated the presence of 0·98 double bond per molecule calc. for $C_8H_{12}$. (Found: C, 88·8; H, 11·4; calc. for $C_8H_{12}$: C, 88·9; H, 11·1%).

The crystalline material was hydrogenated in ether-acetic acid over a Pt catalyst at atmospheric pressure to yield bicyclo[3,2,1]octane, which after repeated sublimation melted at 136–137·5°. Before sublimation infra-red and mass spectrometry indicated the presence of not more than 3% of bicyclo-[2,2,2]octane and 5–6% of ethylcyclohexane. The pure compounds were used as spectroscopic standards.

When the Diels–Alder reaction described above was carried out in the presence of about 1·0% molar of pyridine the white, solid bicyclo[2,2,2]octene was obtained, boiling at 133–135°, m.p. 98–106°; after sublimation from $P_2O_5$ the yield was 20% and m.p. 112–113°.

On heating 10 g bicyclo[2,2,2]octene-2 with 1 g moist ferric chloride for 5 hr at 250°, a mixture of 37% of the [2,2,2]- and 63% of the [3,2,1]-isomer was obtained. The analysis of this mixture was carried out with the aid of mass spectrometry after hydrogenation.

### 2. *Hydration and oxidation of bicyclo*[3,2,1]*octene-2*

The bicyclo[3,2,1]octene-2 crystals m.p. 43–45° were hydrated with diluted sulphuric acid, as described by Newman *et al.*[14] for bicyclo[2,2,2]octene. The reaction product, bicyclo[3,2,1]octanol-2, was sublimed repeatedly, finally from anhydrone. Then its m.p. 187–187·5° and those of its phenyl-urethane (126°) and *p*-nitrobenzoate (79·5–81°) were in agreement with those mentioned in the literature.[13,14] The melting points were not lowered by admixture with bicyclo[3,2,1]octanol-2 and derivatives, respectively, which were prepared from bicyclo[2,2,2]octene-2 according to Newman *et al.*[14]

The oxidation of bicyclo[3,2,1]octene with potassium permanganate was carried out according to the method used by Birch *et al.*[20] A solution of 2 g of the crystals m.p. 43–45° in 10 ml iso-octane was poured while stirring with a vibrating mixer into a 2-litre beaker containing 150 ml water. A solution of 7·5 g potassium permanganate in 225 ml water was added as fast as decolorization occurred; the temp was held below 50°. To keep the solution neutral, a steady stream of carbon dioxide was passed in. After the end of the reaction, sulphur dioxide was passed in to bring the precipitated manganese dioxide into solution. The solution was acidified with sulphuric acid and exhaustively extracted with

[18] e.g. G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.* **77**, 4031 (1955).
[19] Unpublished results by H. M. Walborsky and M. Baum as quoted by A. Streitwieser, *Chem. Rev.* **56**, 571 (1956).
[20] S. F. Birch, J. W. Oldham and E. A. Johnson, *J. Chem. Soc.* 818 (1947).

ether. The ether was dried over sodium sulphate. After evaporation of the ether, a solid residue remained with m.p. 118–130° (2·2 g). Crystallization from benzene yielded 1·8 g (60%) white crystals m.p. 138–139° (lit 139°[15]).

Titration indicated an equivalent weight of 86; calculated for $C_8H_{12}O_4$: 86.

A solution of 1·7 g of the $C_8$ dicarboxylic acid and 2 g $CrO_3$ in 100 ml acetic acid was heated on the steam bath for 3 hr; the solution became green. The acetic acid was removed in vacuo and the solid residue was extracted with ether and recrystallised from benzene. Its m.p., 117–119°, was not depressed on admixture with a pure sample of *cis*-1,3-cyclopentanedicarboxylic acid m.p. 118–119°, obtained by oxidation of norbornene.

3. *Chlorination of bicyclo*[2,2,2]*octane*

5·5 g bicyclo[2,2,2]octane (50 mmoles) was dissolved in 30 ml carbon tetrachloride and brought to 28°. 17 ml 1·805 N $Cl_2$ in $CCl_4$ (15 mmoles) was added and the mixture was irradiated with ultra-violet light. After 2 min it was decolorized and the temp had risen to 33°.

The carbon tetrachloride was removed under reduced pressure and a solid residue of 5·1 g remained. This residue was analyzed by infra-red and mass-spectrometrical methods.

4. *Competitive halogenations of bicyclo*[2,2,2]*octane and cyclohexane*

An example is given of the competitive chlorination of the above cyclanes. A solution of 1·376 g (12·5 mmoles) bicyclo[2,2,2]octane and 1·049 g (12·5 mmoles) cyclohexane in 30 ml carbon tetrachloride was cooled to 5° and 6 ml of a 0·98 N solution of chlorine in carbon tetrachloride was added under ultra-violet irradiation; the temp was kept at 5°. When the reaction was finished, the carbon tetrachloride was distilled under reduced pressure in an eight-plate column until the residue had a volume of about 5 ml. This residue was analysed by gas-liquid chromatography, using a column of dinitrodiphenic acid $C_5$–$C_6$ ester on sterchamol at 140°, with $\beta$-ray detection. Hydrogen was used as the carrier gas.

The integrated peaks for the bicyclo-octyl chloride and cyclohexyl chloride were 297 and 238, respectively.

The relative molar quantities were 279/144·5 = 1·93 and 238/118·5 = 2·01; in other words, the mixture of chlorides contained 49% bicyclo[2,2,2]octyl chloride and 51% cyclohexyl chloride, hence

$$\frac{K_c}{K_b} = \frac{\log\left(1 - \frac{0{\cdot}51 \times 2{\cdot}94}{12{\cdot}5}\right)}{\log\left(1 - \frac{0{\cdot}49 \times 2{\cdot}94}{12{\cdot}5}\right)} = 1{\cdot}04.$$

Bromation experiments were carried out analogously.

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# CHEMISTRY OF THE NATURAL ORDER CUPRESSALES—XXVI*

## THE IDENTITY OF JUNIPENE, KUROMATSUENE AND LONGIFOLENE AND OF JUNIPEROL, KUROMATSUOL, MACROCARPOL AND LONGIBORNEOL

S. AKIYOSHI, H. ERDTMAN and T. KUBOTA
Faculty of Engineering, Kyushu University, Fukuoka, Japan; Kungl. Tekniska Högskolan, Institutionen för organisk kemi, Stockholm, Sweden; Faculty of Science, Osaka City University, Osaka, Japan

(*Received* 27 *November* 1959)

**Abstract**—Kuromatsuene and longifolene are identical with junipene, and kuromatsuol and longiborneol are identical with juniperol.

MATTSON[1] described a sesquiterpene $C_{15}H_{24}$ called junipene and a sesquiterpene alcohol $C_{15}H_{26}O$ called juniperol from the bark of *Juniperus communis* L. The well defined crystals of the latter had already been subjected to a crystallographic study by Ramsay.[2]

Later Shinozaki described a sesquiterpene kuromatsuene isolated from the root oil of *Pinus thunbergii* Parlatore (Kuromatsu)[3] and Akiyoshi isolated both kuromatsuene and a sesquiterpene alcohol, kuromatsuol, from the same tree.[4] These papers have remained almost unknown but it can be seen from Tables 1 and 2 that the physical

TABLE 1

| No | Name | b.p./mm | $n_D$ | $[\alpha]_D$ | M.p. of hydrochloride | M.p. of hydrobromide | Source | References |
|---|---|---|---|---|---|---|---|---|
| 1 | Junipene | 257/767 | 1·5030(20°) | 41·05° | 58·5° | — | Bark of *Juniperus communis* | 1 |
| 2 | Kuromatsuene | 109/7 | 1·5032(20°) | 40·3° | 59–60° | — | Root oil of *Pinus thunbergii* | 3 |
| 3 | Junipene | 115/10 | 1·5032(23°) | 37° | 58–59° | — | Bark of *Juniperus communis* | this work |
| 4 | Kuromatsuene | 127·5–128·5/18 | 1·5043(18·5°) | — | — | 71–72° | Oleoresin of *Pinus densiflora* | unpublished |
| 5 | Longifolene | 254–256/706 150–151/36 | 1·4950(30°) | 42·7° | 59–60° | 69–70° | Various pines | 10 |

constants of kuromatsuene and kuromatsuol are similar to those of Mattson's junipene and juniperol.

During an investigation of the leaf oil of *Cupressus macrocarpa* Hartweg, Briggs and Sutherland[5] isolated the sesquiterpene alcohol macrocarpol, which later was also obtained from the heartwood of *Dacrydium cupressinum*, Solander (Rimu), by Brandt

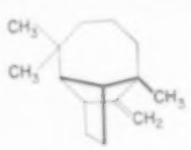
* Part XXV, *Acta Chem. Scand.* in press.

[1] G. Mattson, *Bidr. Finl. Nat. Folk.* **H 72**, 1 (1913).
[2] H. Ramsay, *Z. Kryst. Min.* **46**, 281 (1909).
[3] E. Shinozaki, *J. Ind. Chem. Soc., Japan* 763 (1918).
[4] S. Akiyoshi, *Rep. Imp. Ind. Res. Inst., Osaka, Japan* **17**, No. 10 (1937).
[5] L. H. Briggs and M. D. Sutherland, *J. Org. Chem.* **7**, 397 (1942).

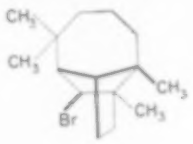
and Thomas.[6] This sesquiterpene alcohol was, subsequently, shown to be identical with juniperol by Erdtman and Thomas.[7]

During the course of an investigation of the sesquiterpene fractions of the oleoresin of *Pinus densiflora* Siebold et Zuccarini (Akamatsu) and of *Pinus Formosana* Hayata, kuromatsuene and kuromatsuol were isolated by one of us (T. K. with T. Tsutsui unpublished. Compare also Ito and Matsumoto).[8] These compounds have now been shown to be identical with junipene and juniperol respectively which were isolated from a sample of the bark oil of *Juniperus communis* L. At the same time a close similarity was noticed between the reported physical constants of longifolene and longiborneol and those of junipene and juniperol.

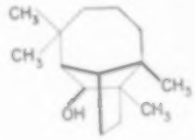
Longiborneol (III) was prepared by Naffa and Ourisson starting from longifolene (I) which was converted into longibornyl bromide (II), and then to the corresponding Grignard compound. This when treated with oxygen in ether yielded longiborneol.[9]



I
Longifolene



II
Longifolene
Hydrobromide



III
Juniperol
(Longiborneol)

Longifolene, longifolene hydrochloride and longiborneol have been compared with junipene, junipene hydrochloride and juniperol. Mixed melting points and a comparison of the infra-red spectra show that longifolene is identical with junipene,

TABLE 2

| No | Name | m.p. | $[\alpha]_D$ | Source | References |
|---|---|---|---|---|---|
| 6 | Juniperol | 107 | 18·4 ($CHCl_3$)<br>17·8 ($C_2H_5OH$) | Bark of *Juniperus communis* | 1 |
| 7 | Kuromatsuol | 107–108 | 12·2 | Root oil of *Pinus thunbergii* | 4 |
| 8 | Macrocarpol | 110 | 25·4 ($C_2H_5OH$) | Leaf oil of *Cupressus macrocarpa* | 5 |
| 9 | Macrocarpol | 112 | 17 ($C_2H_5OH$) | Heartwood of *Dacrydium cupressinum* | 6 |
| 10 | Juniperol | 110 | 16 ($CHCl_3$) | Bark of *Juniperus communis* | this work |
| 11 | Juniperol | 109–110 | 17 ($CHCl_3$) | Oleoresin of *Pinus formosana* | unpublished |
| 12 | Juniperol | 105–109 | — | Oleoresin of *Pinus densiflora* | unpublished |
| 13 | Longiborneol | 106–107 | 21 | From longifolene | 9 |

that longifolene hydrochloride is identical with junipene hydrochloride and that longiborneol is identical with juniperol. Kuromatsuene and kuromatsuol were similarly identified with longifolene and juniperol respectively.

The physical constants of longifolene (junipene, kuromatsuene) and juniperol (kuromatsuol, macrocarpol, longiborneol) from various sources are shown in Tables 1 and 2.

[6] C. W. Brandt and B. R. Thomas, *N.Z. J. Sci. Tech.* **B 33**, 30 (1951).
[7] H. Erdtman and B. R. Thomas, *Chem. & Ind.* 384, (1955).
[8] Sh. Ito and T. Matsumoto, *Chem. Abstr.* **49**, 15236 (1955).
[9] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* **5**, 1410 (1954); A. Hesse, *Ber. Dtsch. Chem. Ges.* **39**, 1151 (1906).
[10] J. L. Simonsen, *The Terpenes* Vol. III, p. 92. Cambridge (1952).

Direct comparisons have been carried out on the following samples: 3 and 5, 4 and 5 (this work); 6 and 9;[7] 8 and 9;[6] 10 and 11; 10, 11 and 13 (this work); 11 and 12 (as 3,5-dinitrobenzoates).

No direct comparison with the products obtained from *P. thunbergii* by Akiyoshi could be made, since these samples were lost during the war. The optical rotation of the juniperol preparations varies considerably. Although juniperol crystallizes well it seems difficult to obtain absolutely pure.

Mattson's name junipene has priority over longifolene which was described by Simonsen in 1920, but it is suggested that the well known name longifolene should be retained for this compound. For the alcohol the name juniperol, as suggested earlier,[7] should be retained instead of macrocarpol (and kuromatsuol and longiborneol).

From a chemotaxonomic point of view it is of interest to note that longifolene is represented in the natural orders Pinales, Cupressales and Podocarpales. A biosynthetic relation between longifolene and juniperol appears, of course, to be very probable since they frequently occur together in the same tree.

*Acknowledgements*—The authors would like to thank the U.S. Army and Development Liaison Group under contract number DA-91-591-EUC-1113 for the grant which enabled one of us (T. K.) to take part in this work. We also wish to thank Professor and Mrs. Sörensen, Trondheim and Professor Ourisson for samples of the bark oil of *Juniperus communis* and of longifolene, its hydrochloride and longiborneol.

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# AROMATIC POLYFLUORO-COMPOUNDS—V*

## THE PREPARATION OF HIGHLY FLUORINATED BENZENES BY DEFLUORINATION OF POLYFLUOROCYCLOHEX-ANES, -ENES, AND -DIENES

P. L. Coe, C. R. Patrick and J. C. Tatlow
Chemistry Department, The University, Birmingham

(*Received* 4 *December* 1959)

**Abstract**—Hexa-, penta- and tetra- fluorobenzenes are formed from appropriate polyfluorocyclohex-anes, -enes and -dienes by passage in vapour form over heated iron gauze.

In previous communications[1,2] we have described a new general method for the preparation of perfluoro-aromatic compounds by the defluorination of cyclic aliphatic fluorocarbons. The method consists in passing the compound to be defluorinated, in the vapour phase, in a stream of nitrogen, over a heated metal, usually iron or nickel gauze, packed into a tubular reaction vessel.[2] The metal fluoride which is produced in the defluorination process forms an impervious deposit on the metal surface and eventually prevents further reaction. The metal needs, therefore, to be regenerated, and this may conveniently be done by reduction of the metal fluoride with hydrogen. In this paper we describe the extension of this method of defluorination to the preparation of hexafluorobenzene from dodecafluorocyclohexane and from decafluorocyclohexene, and to the preparation of other highly fluorinated benzenes, particularly of pentafluorobenzene, from various fluorocyclohex-enes and -dienes.

The formation of perfluoroaromatic compounds by the defluorination of saturated materials depends on the greater stability of the aromatic compounds to the defluorination conditions. Thus, at low temperatures, depending on the contact time but generally about 350° or less, no defluorination of alicyclic compounds takes place, whereas at high temperatures, about 750° or more, fluorocarbon material is completely broken down, presumably to give metal fluoride and carbon. Simple considerations, therefore, suggest that for each compound investigated there should be a reaction contact time and reactor temperature for which the yield of the desired aromatic compound is optimal. These reaction conditions will, in addition, be determined by the geometry of the reactor and its packing, and also by the age and previous treatment of the packing. The effect of temperature on the defluorination process is illustrated by the results on the defluorination of decafluorocyclohexene[3] (Table 1). These results show that the most economical temperature for the production of hexafluorobenzene in the reactor used was about 550°. At this temperature the total recovery of material by weight was about 70 per cent, and about 46 per cent of the starting material was converted to hexafluorobenzene.

* Part IV: *J. Chem. Soc.* In press.

[1] B. Gething, C. R. Patrick, J. C. Tatlow, R. E. Banks, A. K. Barbour and A. E. Tipping, *Nature, Lond.* **183**, 586 (1959).
[2] B. Gething, C. R. Patrick, M. Stacey and J. C. Tatlow, *Nature, Lond.* **183**, 588 (1959).
[3] A. K. Barbour, H. D. Mackenzie, M. Stacey and J. C. Tatlow, *J. Appl. Chem.* **4**, 347 (1954).

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It has been found possible to defluorinate dodecafluorocyclohexane[4] to give hexafluorobenzene. Decafluorocyclohexene is also a product of the reaction, particularly at relatively low temperatures. This observation demonstrates the stepwise nature of the defluorination process. The failure to observe octafluorocyclohexadienes in the reaction products is obviously the consequence of the extreme instability of these compounds to the defluorination conditions needed to defluorinate more nearly

TABLE 1. EFFECT OF TEMPERATURE ON THE DEFLUORINATION OF DECAFLUOROCYCLOHEXENE

Nitrogen flow rate 2 l/hr. Charge of $C_6F_{10}$, 16·6 g in each case. Only $C_6F_{10}$ and $C_6F_6$ were found in the products.

| Reactor temperature (°C) | Weight of material recovered (g) | % $C_6F_6$ in product |
|---|---|---|
| 490 | 13·17 | 11·7 |
| 510 | 12·44 | 36·1 |
| 530 | 11·15 | 43·6 |
| 550 | 10·91 | 62·9 |
| 580 | 8·43 | 73·0 |
| 600 | 6·58 | ca 100 |

TABLE 2. DEFLUORINATION OF DODECAFLUOROCYCLOHEXANE

| Temperature (°C) | Flow rate (l/hr) | Input (g) | Yield (g) | Wt. of products isolated (g) $C_6F_{12}$ + $C_6F_{10}$ | Wt. of products isolated (g) $C_6F_6$ |
|---|---|---|---|---|---|
| 630 | 8 | 6·5 | 4·3 | 2·5 | 0·5 |
| 590 | 6 | 5·5 | 2·7 | 1·1 | 1·0 |
| 590 | 4 | 21 | 9·5* | 4·4* | 1·6* |

* In this experiment only 7·2 g of the mixed product was carried forward to separation. The weight of product reported as $C_6F_{12}/C_6F_{10}$ contained 0·2 g of $C_6F_{10}$.

saturated compounds. Octafluorocyclohexadienes[5] have been found to give hexafluorobenzene almost exclusively and in good yield (over 90 per cent) at temperatures between 400 and 450° using nitrogen flow rates of 2 litres/hr. Reactor temperatures greater than about 550° were found to be necessary for the defluorination of decafluorocyclohexene and dodecafluorocyclohexane.

Early experiments showed that the defluorination process was not limited in its application to compounds containing only carbon and fluorine. Thus, 1H-heptafluorocyclohexa-1,3-diene[6] was found to give pentafluorobenzene together with

[4] R. P. Smith and J. C. Tatlow, *J. Chem. Soc.* 2505 (1957).
[5] D. E. M. Evans and J. C. Tatlow, *J. Chem. Soc.* 1184 (1955).
[6] J. Godsell, M. Stacey and J. C. Tatlow, *Tetrahedron* **2**, 193 (1958).

hexafluorobenzene which was probably produced by the dehydrofluorination of 5H-heptafluorocyclohexa-1,3-diene or a similar structure formed by the isomerization of the starting material. 1,3- and 1,4-Dienes isomerize readily when heated.[1] Since hexafluoro- and pentafluoro-benzene may easily be separated by preparative scale gas chromatography the defluorination reaction affords a convenient method for the preparation of the pentafluoride. Further investigations have been made of the

Table 3. Defluorination of mixed octafluorocyclohexadienes
Results calculated for charges of 16·6 g

| Temperature (°C) | Flow rate (l/hr) | Weight of material recovered (g) |
|---|---|---|
| 450 | 4 | 12·6* |
| 500 | 4 | 10·8 |
| 540 | 4 | 10·6 |
| 580 | 4 | 9·2 |
| 600 | 4 | 5·7 |
| 400 | 2 | 12·0 |
| 450 | 2 | 10·7 |
| 470 | 2 | 9·8 |
| 500 | 2 | 8·8 |

Except where indicated, the recovered material was almost pure hexafluorobenzene.

These results indicate that an increase in reaction time brought about by reduction of the flow rate reduces the temperature required to give optimum yields of aromatic products.

* This product contained about 10 per cent starting material.

Table 4. Defluorination of heptafluorocyclohexadienes
Variation of products with temperature of the body of the reactor. Flow rate 2 l. nitrogen/hr. Charge 16·6 g.

| Temperature (°C) | Weight of material recovered* (g) | % $C_6F_5H$ |
|---|---|---|
| 390 | 12·1 | 57 |
| 400 | 12·1 | 60 |
| 420 | 12·1 | 68 |
| 450 | 12·0 | 64 |
| 460 | 9·9 | 65 |
| 480 | 10·5 | 64 |
| 500 | 9·9 | 61 |

* The recovered product contained only hexafluoro- and pentafluorobenzene in all cases.

defluorination of heptafluorocyclohexadienes, and it has been found that over a wide range of reactor temperatures the ratios of the amounts of pentafluorobenzene to hexafluorobenzene in the products were close to two to one, although the overall yield

of these compounds decreased at temperatures above about 450° using nitrogen flow rates of 4 litres/hr. It was found, however, that the composition of the reaction products was influenced by the distribution of temperature in the reactor, rather than by the temperature of the central and most extensive zone of the reactor. This point is illustrated by the results presented in Table 5, which were obtained by the

TABLE 5. DEFLUORINATION OF MIXED HEPTAFLUOROCYCLOHEXADIENES USING VARIOUS REACTOR CONDITIONS

Nitrogen flow rate 4 l/hr. Charge of dienes 16·6 g in each case.

| Reactor temperature (°C) | | | | | Weight of material recovered (g) | | |
|---|---|---|---|---|---|---|---|
| Section No. | | | | | Total | $C_6F_6$ | $C_6F_5H$ |
| 1 | 2 | 3 | 4 | 5 | | | |
| 120† | 460 | 460 | 460 | 130 | 12·6 | 5·1 | 5·1 |
| 345 | 460 | 460 | 460 | 390 | 13·5 | 6·8 | 3·2 |
| 460 | 460 | 460 | 400 | 380 | 10·3 | 1·6 | 6·2* |
| 460 | 460 | 460 | 400 | 380 | 10·7 | 1·8 | 6·1 |

* The products of this run also included 0·7 g of 1,2,4,5-tetrafluorobenzene. The starting material was found to be free of dienes containing two hydrogen atoms, and the tetrafluorobenzene presumably resulted from reduction by hydrogen adsorbed in the reactor. Similar observations have been made in some other cases and the effect is being investigated further.

† Presumably in this case the temperature in the first section is too low to produce much reaction.

defluorination of the mixture of heptafluorocyclohexadienes, prepared by the dehydrofluorination of 1H, 2H, 4H-nonafluorocyclohexane,[6] and which contained 1H-heptafluorocyclohexa-1,4-diene (about two parts), 1H-heptafluorocyclohexa-1,3-diene (about one part) and 2H-heptafluorocyclohexa-1,3-diene (about one part). These results show that higher temperatures in the first part of the reactor to be encountered by the starting material favour the formation of pentafluorobenzene relative to hexafluorobenzene. This effect may be understood in terms of the competition between isomerization and defluorination as the first process in the reaction system. If a mixture of dienes is subjected first to temperatures that are too low to enable defluorination to take place, the more facile isomerization may proceed to produce compounds in which hydrogen is attached to saturated carbon atoms, and these will readily lose hydrogen fluoride to give, from heptafluorocyclohexadienes, hexafluorobenzene. At higher temperatures defluorination of the dienes will proceed more readily to give pentafluorobenzene, and will reduce the proportion of hexafluorobenzene in the product.

The competition between isomerization and defluorination as first reaction steps, also accounts for the effects observed on passing successive samples of mixed heptafluoro-1,3- and 1,4-dienes through the reactor without removal of the metal fluoride by hydrogenation between the runs. The product obtained from the defluorination of a second aliquot of the mixed dienes contained 40 per cent pentafluorobenzene and

60 per cent hexafluorobenzene, whereas the first aliquot produced 60 per cent pentafluorobenzene and 40 per cent hexafluorobenzene. The difference between the products is due to the formation of a fluoride deposit on the metal in the first run so as to reduce the ease of defluorination, and so raise the probability of isomerization as first reaction step in the second run. It is for this reason that the use of large aliquots produces lower yields of pentafluorobenzene.

The defluorination reaction was applied to mixed 1H,2H-hexafluorocyclohexa-1,4- and 1,3-dienes[7] to give a mixture of pentafluorobenzene and 1,2,3,4-tetrafluorobenzene, the first compound arising presumably from the dehydrofluorination of an isomer of the starting material produced under the reaction conditions.

The defluorination of 4H-nonafluorocyclohexene[5] yielded both pentafluorobenzene and hexafluorobenzene, but mainly the former. Thus, at 450° using a nitrogen flow rate of 2 litres/hr, the products of the reaction were pentafluorobenzene (33 per cent), and hexafluorobenzene (10 per cent), both calculated on the basis of yield from starting material. The hexafluorobenzene is produced by the successive dehydrofluorination and defluorination of the starting material. It is noteworthy that the temperatures required to defluorinate nonafluorocyclohexene (450–500°) are lower than those required to defluorinate decafluorocyclohexene (550–600°), and probably reflect the lower strength of C—F bonds in >CHF groups relative to those in $>CF_2$ groups.

Undecafluorocyclohexane[3] was found on pyrolytic defluorination to give hexafluorobenzene and pentafluorobenzene. The first of these compounds, whose formation involves dehydrofluorination, was formed in the greater yield.

Table 6. Defluorination of 1H,4H-octafluorocyclohex-1-ene
Runs at 2 l. nitrogen/hr. 8·2 g charge. The product contained 1,2,4,5-tetrafluorobenzene in all cases.

| Temperature (°C) | Yield (g) | % $C_6F_6$ | % $C_6F_5H$ | % $C_6F_4H_2$ |
|---|---|---|---|---|
| 420 | 4·5 | 15 | 54 | 15 |
| 480 | 4·3 | 24 | 33 | 21 |
| 550 | 3·3 | 15 | 37 | 26 |

The defluorination of 1H,4H-octafluorocyclohexene[7] has been found to produce 1,2,4,5-tetrafluorobenzene, pentafluorobenzene and hexafluorobenzene. Also, as noted for the case of nonafluorocyclohexene, the temperatures needed for the reaction of this compound (about 450°) are lower than those required for the defluorination of decafluorocyclohexene. A similar reaction with 4H/5H-octafluorocyclohexene[6] has been found to give 1,2,3,4-tetrafluorobenzene together with some pentafluoro- and hexafluoro-benzene.

In the course of this work the metal packing used in the reactors was iron gauze. As an alternative packing the use of nickel shot was tried, but this gave erratic results, and examination after a short period of use showed that the shot had sintered together so as to favour channelling of the gas passed through the reactor, and the packing could be removed from the reactor only with considerable difficulty. It was also

[7] R. Stephens, J. C. Tatlow and E. H. Wiseman, *J. Chem. Soc.* 148 (1959).

observed that saturated fluoro-compounds were not readily defluorinated by a packing of new iron gauze, but the efficiency of the packing at first increased with use, and then became steady. This ageing effect was not so marked in respect of defluorination of the octafluorocyclohexadienes.

## EXPERIMENTAL

*Apparatus.* The reactors used in this investigation were the same as those described elsewhere[8] and consisted of nickel tubes of diameter 2½″ and length 4′ mounted in horizontal furnaces and packed with iron gauze. The furnaces, which were of the same length as the reactor tubes, consisted of five heating sections of equal length. The flow rate of the incoming gas stream was measured on a rotameter. The samples were volatilized into the stream of nitrogen in a heated section of glass tubing close to the furnace. The reaction products were collected in traps immersed in liquid oxygen, and were separated by use of preparative scale chromatography.[8] After each run, except where otherwise indicated, the metal fluoride formed in the reactor was removed by passage of a stream of hydrogen flowing at 10–20 litre/hr for 30 min, followed by a stream of nitrogen flowing at 8 litre/hr for a further 30 min.

*Defluorination of successive charges of mixed heptafluoro-cyclohexadienes without intermediate removal of fluoride layer*

The mixed heptafluorodienes (16·5 g) were passed in a stream of nitrogen at 4 litres/hr through the reactor heated in the various sections to 460°, 460°, 460°, 400°, and 380° respectively from the inlet end. The product (11·6 g) contained hexafluorobenzene (37%) and pentafluorobenzene (63%). A second charge of dienes passed through the reactor under the same conditions gave a product (11·2 g) containing hexafluorobenzene (61%) and pentafluorobenzene (39%).

*Defluorination of* 1H,2H-*hexafluorocyclohexa*-1,4- *and* -1,3- *diene*

A mixture of the dienes (8 g) was passed through the reactor at 450° in a stream of nitrogen at 2 litre/hr. The product (5·3 g) contained pentafluorobenzene (49%) and 1,2,3,4-tetrafluorobenzene (51%).

*Defluorination of* 4H-*nonafluorocyclohexene*

The 4H-nonafluorocyclohexene (16 g) was passed through the reactor at 450° in a stream of nitrogen flowing at 2 litre/hr. The product (12·2 g) contained hexafluorobenzene (10%), pentafluorobenzene (33%), and unchanged starting material.

*Defluorination of* 4H/5H-*octafluorocyclohexene*

The 4H/5H-octafluorocyclohexene (8·2 g) was passed through the tube at 520° in a stream of nitrogen flowing at 2 litre/hr. The product (1·74 g) contained 1,2,3,4-tetrafluorobenzene (87%) and a mixture of hexafluoro- and pentafluoro-benzene (13%).

*Defluorination of undecafluorocyclohexane*

Undecafluorocyclohexane (5 g) was passed through the reactor, maintained at 530°, in a stream of nitrogen flowing at 2 litre/hr. The product (1 g) was found to contain decafluorocyclohexene (17%), hexafluorobenzene (50%) and pentafluorobenzene (33%).

*Identification of products*

Products were identified by analytical gas chromatography and by the identity of the infra-red spectra of the pure components with those of authentic specimens. The 1,2,3,4-tetrafluorobenzene was identical with material synthesized by Wall[9] and with a specimen made here by an independent route.[10]

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[8] D. E. M. Evans, W. E. Massingham, M. Stacey and J. C. Tatlow, *Nature, Lond.* **182**, 591 (1958).
[9] W. J. Pummer, R. E. Florin and L. A. Wall, *J. Res. Nat. Bur. Stand.* **62**, 113 (1959).
[10] E. Nield, R. Stephens and J. C. Tatlow, *J. Chem. Soc.* forthcoming publication.

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# ORGANIC REACTIONS IN STRONG ALKALIS—IV

## REARRANGEMENT AND FISSION OF ACIDS WITH α-GLYCOL AND OTHER VICINAL OXYGEN FUNCTIONS

R. A. DYTHAM and B. C. L. WEEDON
Department of Chemistry, Imperial College of Science and Technology, London

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**Abstract**—On treatment with strong alkalis, 9,10-dihydroxystearic acid, and the corresponding hydroxy-keto and diketo acids, give α-octyl-α-hydroxysebacic acid in high yield by a benzilic acid type of rearrangement. Under more vigorous conditions 9-oxoheptadecanoic acid is formed, which then hydrolyzes to give octanoic, nonanoic and azelaic acids as the main products.

10,11-Dihydroxyundecanoic, 9,10,12-trihydroxyoctadecanoic and aleuritic acids undergo analogous fission reactions on alkali fusion.

IN the preceding paper[1] we described the reactions of monohydroxy fatty acids in concentrated alkalis. We are concerned here with the behaviour of some dihydroxy-derivatives of unsaturated fatty acids, and related compounds containing vicinal oxygen functions.

In 1914 Le Sueur and Withers[2] reported that treatment of (erythro-) 9,10-dihydroxystearic acid (I) with concentrated potassium hydroxide at 200–250° gave 65 per cent of α-hydroxy-α-octylsebacic acid (II) and, by further reaction of the latter with alkali, ca. 2 per cent of 9-oxoheptadecanoic acid (III). At higher temperatures (up to 275°) some nonanoic and azelaic acid were formed. Analogous results were also obtained with 13,14-dihydroxybehenic acid. These careful studies seem to have been overlooked by most subsequent workers who have simply reported that alkaline fission of 9,10-dihydroxystearic acid gives nonanoic and azelaic acid.[3–6] Eckert[3] claimed that the yields were improved by the addition of potassium chlorate to the

$$CH_3\cdot(CH_2)_7\cdot CH(OH)\cdot CH(OH)\cdot(CH_2)_7\cdot CO_2H \quad \text{I}$$

$$CH_3\cdot(CH_2)_7\cdot C(OH)\cdot(CH_2)_7\cdot CO_2H \quad \text{II}$$
$$\quad\quad\quad

reaction mixture, and that similar degradations of 9,10,12,13-tetra- (IV) and 9,10,12,13,15,16-hexa-hydroxystearic acid (V), derived from linoleic and linolenic acids, gave azelaic, acetic and either hexanoic or propionic acid respectively. According to Logan,[4] alkaline fission of (threo-) 9,10-dihydroxystearic acid with 70 per cent sodium hydroxide also yields nonanol and an $\omega$-hydroxy-acid, presumably 10-hydroxynonanoic acid, though no information on the properties of the product, or its isolation, have been given.

In the present studies alkali fusion of both erythro- and threo- 9,10-dihydroxystearic acid at 300–360° gave almost identical mixtures of acids (Table 1). In agreement with earlier reports the dicarboxylic acids consisted very largely of azelaic, but,

TABLE 1. ALKALI FUSION OF 9,10-DIHYDROXYOCTADECANOIC AND RELATED ACIDS

(1 hr; yield of acidic products in moles)

| Acidic products | | Threo-dihydroxy acid | | | Erythro-dihydroxy acid | Hydroxy-keto acids | 9-Oxoheptadecanoic acid | |
|---|---|---|---|---|---|---|---|---|
| | | *300°* | *300°* | *360°* | *360°* | *300°* | *300°* | *300°* |
| Mono-carboxylic acids | n-$C_7$ | 0·06 | 0·12 | 0·06 | 0·04 | 0·06 | 0·06 | 0·10 |
| | n-$C_8$ | 0·26 | 0·20 | 0·22 | 0·22 | 0·20 | 0·19 | 0·26 |
| | n-$C_9$ | 0·34 | 0·30 | 0·33 | 0·29 | 0·30 | 0·40 | 0·40 |
| | "Me-$C_{15}$"[a] | 0·03 | 0·03 | 0·05 | 0·04 | 0·06 | 0·04 | — |
| | "Me-$C_{17}$"[a] | trace | trace | — | — | — | 0·04 | 0·05 |
| High b.p. acids[b] | | 0·20 | 0·18 | 0·18 | 0·27 | 0·17 | 0·17 | 0·10 |
| Di-carboxylic acids | n-$C_7$ | 0·03 | 0·03 | 0·05 | 0·03 | 0·04 | 0·04 | 0·03 |
| | n-$C_9$ | 0·34 | 0·33 | 0·40 | 0·34 | 0·41 | 0·38 | 0·41 |

[a] "Me-$C_{15}$" signifies 7-methylpentadecanoic acid and "Me-$C_{17}$" a mixture of 9-methylheptadecenoic acids. These products are formulated by analogy with those from other keto-acids (Part III).

[b] Approximate value estimated by difference.

surprisingly, the mono-carboxylic acids contained almost as much octanoic as nonanoic acid. Repetition of the reaction at 260–270° gave, in addition to the above fission products, 9-oxoheptadecanoic acid (III) in yields up to 30 per cent. At still lower temperatures (230–240°), α-hydroxy-α-octylsebacic acid (II) was obtained in yields up to 90 per cent together with traces of nonanoic and azelaic acid. Alkali fusion of the keto-acid at 300° gave the mixture of acids expected by analogy with 10- and 12- ketostearic acid (Part III),[1] the principal products being azelaic, by hydrolysis of the 9,10 bond, and both octanoic and nonanoic acid by fission of the 8,9-bond (Table 1). Considered in conjunction with the results of Le Sueur and Withers, the above transformations, and the close similarity between the final products from 9-oxoheptadecanoic acid and those from the dihydroxystearic acids, clearly indicate that fission of the latter proceeds by the successive formation of the hydroxy-dicarboxylic acid (II) and the keto-acid (III).

In 1922 Nicolet and Jurist[7] demonstrated that 9,10-diketostearic acid (VI) underwent a benzilic acid rearrangement on treatment with molten alkali to give

[7] B. H. Nicolet and A. E. Jurist, *J. Amer. Chem. Soc.* **44**, 1136 (1922).

α-hydroxy-α-octylsebacic acid (II), and suggested that the diketo-acid is an intermediate in the conversion of 9,10-dihydroxystearic acid into the same product (II). Since it has recently been demonstrated (Part III)[1] that mono-hydroxy acids are smoothly converted into keto-acids in molten alkali, a dehydrogenation of 9,10-dihydroxystearic acid to give successively the corresponding α-hydroxy-ketones and α-diketone, or related ionic species, seems plausible. Although Nicolet and Jurist[7] obtained α-hydroxy-α-octylsebacic acid in only 12 per cent yield from 9,10-diketostearic acid, repetition of their experiment (in an inert atmosphere) raised the yield to 70 per cent; small amounts (4 per cent) of nonanoic and azelaic acid were also detected.*

As expected, alkali fusion of an authentic mixture of 9-hydroxy-10-oxo- and 10-hydroxy-9-oxo-octadecanoic acids (VIIa and b) at 300° gave a product very similar in composition to that obtained from the corresponding dihydroxy acids under similar conditions. At 230° the main product (52 per cent), as from the dihydroxy-acids, was α-hydroxy-α-octylsebacic acid (II); small amounts (12 per cent) of nonanoic and azelaic acid, and traces (2 per cent) of octanoic acid, were also detected. Hilditch and Plimmer[8] have previously demonstrated the fission of the mixture of hydroxy-oxo-octadecanoic acids to nonanoic and azelaic acid in 50 per cent alcoholic alkali at 50°. We find that, at slightly higher temperatures (ca. 80°), α-hydroxy-α-octylsebacic acid is also produced.

As mentioned above, small amounts of nonanoic and azelaic acid are formed from the dihydroxy-, hydroxy-keto-, and diketo-stearic acids under conditions which favour the production of α-hydroxy-α-octylsebacic acid. It is noteworthy that octanoic acid is either absent from the products, or obtained in much smaller amounts than nonanoic and azelaic acid. This indicates that (in an inert atmosphere) octanoic acid is formed by conversion of α-hydroxy-α-octylsebacic acid into 9-oxoheptadecanoic acid, and subsequent hydrolysis, but that, under conditions too mild for the breakdown of the α-hydroxy-diacid, nonanoic and azelaic acid are still formed by fission of the hydroxy-keto- and diketo-stearic acids, and dehydrogenation of the initially formed alcohols or aldehydes. Such dehydrogenations are believed to involve hydride ion transfers, and it has been shown that ketones can act as acceptors in these reactions (cf. Part III). This suggests an obvious explanation for the reported formation of dihydroxystearic acid as a by-product during the reaction of the hydroxy-keto-[8] and the diketo-stearic acids[7] with alkalis.

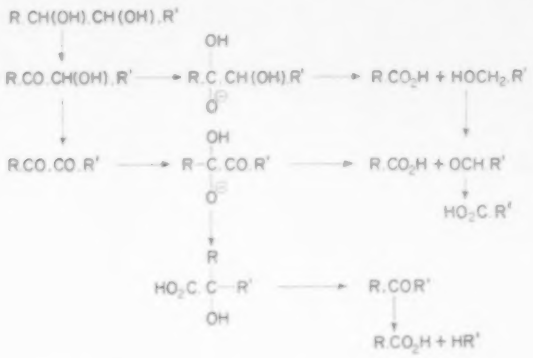
Treatment of threo-9,10-dihydroxyoctadecanoic acid under conditions similar to those stated by Logan[4] to give nonanol and an "ω-hydroxy acid" gave α-hydroxy-α-octylsebacic acid (II) in 60 per cent yield. Repetition of the reaction in an atmosphere of oxygen (claimed[4] to favour the formation of alcohols) gave a small amount of a volatile product whose three main components were identified as n-nonanol, n-nonanal, and n-octanol by mixed gas-liquid chromatograms with authentic specimens; both octanoic and suberic acid were also detected in addition to the usual fission products. The use of an oxygen atmosphere thus appears to promote oxidation of the dihydroxystearic acid, but other reactions (probably involving oxidative cleavage of ketones,[9] or oxygenation of carbanion intermediates[1]) clearly intrude.

* Dr. J. F. McGhie has kindly informed us of results obtained in his laboratory which are in good agreement with ours. We are also indebted to him for samples of both the hydroxy-keto and diketo acids.

[8] T. P. Hilditch and H. Plimmer, *J. Chem. Soc.* 204 (1942); cf. R. S. Morrell and E. O. Phillips, *J. Soc. Chem. Ind.* **57**, 245 (1938).

[9] W. von E. Doering and R. M. Haines, *J. Amer. Chem. Soc.* **76**, 482 (1954).

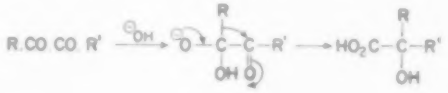
The principal reactions discussed above are summarized in Scheme 1. The mechanisms of the dehydrogenations and hydrolyses are doubtless similar to those




R and R' represent the two different end groups, viz. $CH_3.(CH_2)_7$ or $(CH_2)_7.CO_2H$.

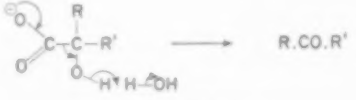
Scheme 1.

of simple hydroxy and keto compounds (Part III). The formation of α-hydroxy-α-octylsebacic acid from 9,10-diketostearic acid may be regarded as a rearrangement of the benzilic acid type (Scheme 2). The conversion of the hydroxy-octylsebacic acid into 9-oxoheptadecanoic acid involves fission of a carbon–carbon bond; carbon

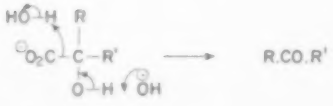



Scheme 2.

dioxide or a carbonate (e.g. Scheme 3) or a formate (Scheme 4) may be the other product formed initially in this process.




Scheme 3.




Scheme 4.

As reported by Logan,[4] alkaline fission of 10,11-dihydroxyundecanoic acid (VIII) gave sebacic acid (90 per cent); small amounts of suberic (2 per cent) and nonanoic acid (5 per cent) were also detected.

$$HOCH_2{\cdot}CH(OH){\cdot}(CH_2)_8{\cdot}CO_2H \rightarrow HO_2C{\cdot}(CH_2)_8{\cdot}CO_2H \qquad \text{(VIII)}$$

Logan also reported[4] that alkali fusion of 9,10,12-trihydroxystearic acid (IX), derived from ricinoleic acid, gave a mixture of azelaic acid, sebacic acid and what appeared to be hexanoic acid with small amounts of nonanoic acid. Repetition of this reaction during the present studies gave no hexanoic or sebacic acids, though heptanoic, octanoic and azelaic acids were obtained (Table 2), as expected by analogy

TABLE 2. ALKALI FUSION OF 9,10,12-TRIHYDROXYOCTADECANOIC ACID
(1 hr; yield of $C_9$ and lower acids in moles)

| Acidic products | | 300° | 300° |
|---|---|---|---|
| Mono-carboxylic acids | n-$C_7$ | 0·25 | 0·32 |
| | n-$C_8$ | 0·08 | 0·12 |
| | n-$C_9$ | 0·04 | 0·04 |
| Di-carboxylic acids | n-$C_8$ | 0·13 | 0·11 |
| | n-$C_9$ | 0·47 | 0·46 |

with the fission products of 12-hydroxy-[3] and 9,10-dihydroxy-stearic acids. However, compared with the fission of the latter acid, the formation of azelaic acid was strongly favoured at the expense of octanoic acid. This difference is not surprising. In view of the oxygen function at $C_{(12)}$, the reaction of 9,10,12-trihydroxystearic acid doubtless involves $\beta$-hydroxy-ketone (e.g. X) or $\beta$-diketone intermediates. It is therefore to be expected that fission at positions corresponding to the 10,11 and 11,12 bonds in the starting material will predominate. Initial dehydrogenation of the $C_{(12)}$ hydroxyl group, and fission to give an intermediate of type XI and octan-2-one, would also favour the formation of azelaic acid. A neutral product formed during treatment of

$$CH_3\cdot(CH_2)_5\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot CH(OH)\cdot(CH_2)_7\cdot CO_2H \qquad IX$$

$$CH_3\cdot(CH_2)_5\cdot CO_2H + HO_2C\cdot(CH_2)_7\cdot CO_2H$$

$$CH_3\cdot(CH_2)_5\cdot CH(OH)\cdot CH_2\cdot CO\cdot(CH_2)_7\cdot CO_2H \qquad X$$

$$OCH\cdot CH(OH)\cdot(CH_2)_7\cdot CO_2H \qquad XI$$

9,10,12-trihydroxystearic acid with strong alkalis was shown chromatographically to contain octan-2-ol and small amounts of octan-2-one. Since the mixture had only weak optical activity, and the $C_{(12)}$ centre in the starting material was that known to be asymmetric in ricinoleic acid, it can be concluded that the octan-2-ol was formed mainly by reduction of octan-2-one produced initially, and not by direct fission. This is consistent with a dehydrogenation of the $C_{(12)}$ hydroxyl group prior to fission.

Two other products, nonanoic and suberic acid, were detected chromatographically after alkali fusion of 9,10,12-trihydroxystearic acid (IX). The former is conceivably an artefact (resulting from contamination of the starting material with 9,10-dihydroxystearic acid) but may arise by dehydration of a $\beta$-hydroxy-ketone (e.g. X), reduction of the resulting $\alpha\beta$-unsaturated ketone (cf. reduction of $\alpha\beta$-unsaturated acids,[10]) and fission. Several tentative explanations can be advanced for

[10] R. G. Ackman, R. P. Linstead, B. J. Wakefield and B. C. L. Weedon, *Tetrahedron* **8**, 221 (1960); R. G. Achman, R. A. Dytham, B. J. Wakefield and B. C. L. Weedon, *Tetrahedron* **8**, 239 (1960).

the production of suberic acid. Perhaps the most plausible at present is the formation of an $\alpha\beta$-unsaturated aldehyde or acid from an intermediate of the type XI, and subsequent fission.

Some preliminary studies have also been made on the alkali fusion of the natural trihydroxy-acid, ($\beta$-) aleuritic acid (XII). In addition to a (threo) $\alpha$-glycol system, this starting material has a primary alcohol grouping which can undergo dehydrogenation in strong alkalis to give a carboxyl function.[1] At 300° hexanoic, octanoic, pimelic and azelaic acids, the expected fission products, were formed in approximately equimolecular amounts (Table 3). However a branched chain or cyclic dicarboxylic

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TABLE 3. ALKALI FUSION OF 9,10,16-TRIHYDROXYHEXADECANOIC ACID
(1 hr; yield of $C_9$ and lower acids in moles)

| Acidic products | | 300° | 300° | 300° | 300° | 300°[a] |
|---|---|---|---|---|---|---|
| Mono-carboxylic acids | n-$C_6$ | 0·16 | 0·23 | 0·14 | 0·19 | 0·22 |
| | n-$C_8$ | 0·18 | 0·23 | 0·13 | 0·16 | 0·20 |
| Di-carboxylic acids | n-$C_7$ | 0·17 | 0·22 | 0·15 | 0·16 | 0·22 |
| | n-$C_9$ | 0·15 | 0·24 | 0·14 | 0·17 | 0·23 |

[a] Reaction time 2·5 hr.

acid of higher molecular weight was formed simultaneously in yields up to 40 per cent. The structure of this acid has not yet been determined. From reactions at 250° two products were isolated in poor yield and tentatively formulated as XIII and XIV by analogy with intermediates derived from 9,10-dihydroxystearic acid.

$$HOCH_2\cdot(CH_2)_5\cdot CH(OH)\cdot CH(OH)\cdot(CH_2)_7\cdot CO_2H \qquad \text{XII}$$

$$HOCH_2\cdot(CH_2)_5\cdot C(OH)\cdot(CH_2)_7\cdot CO_2H \qquad \text{XIII}$$
$$\quad\quad\quad

Natural ($\beta$-) aleuritic acid (kindly supplied by Messrs. Boake Roberts and Co. Ltd.) was crystallized from aqueous methanol and had m.p. 100–101° (lit,[16] m.p. 100°).

### *α-Hydroxy-α-octylsebacic Acid*

(a) *From threo-9,10-dihydroxyoctadecanoic acid*

(i). The dihydroxy-acid (3·5 g) and a finely powdered mixture of potassium and sodium hydroxides (1:1, 10 g) were heated for 1 hr at 230–240° (bath temp). The mixture was cooled and dissolved in water. The solution was acidified, and the product was isolated with ether in the usual way. Crystallization from chloroform–light petroleum (b.p. 40–60°) gave α-hydroxy-α-octylsebacic acid (3·3 g), m.p. 110–111° (lit,[5] m.p. 111°) (Found: C, 65·55; H, 10·55. Calc. for $C_{18}H_{34}O_5$: C, 65·4; H, 10·35%). Permanganate oxidation[5] gave 9-oxoheptadecanoic acid, m.p. 79·5–80·5° (lit,[5] m.p. 78·5°); methyl ester, m.p. 43–44° (lit, m.p. 44°), undepressed on admixture with the specimen described below.

In other reactions of the dihydroxy-acid with molten alkalis at temperatures ranging from 200–260°, the yield of hydroxy-diacid varied from 40–80%.

(ii). The dihydroxy-acid (4·6 g) was heated with a solution of potassium hydroxide (12 g) in water (20 cc) in a nitrogen filled stainless steel autoclave at 300° for 2 hr. When the autoclave was opened, after it had been cooled, hydrogen was released. Isolation of the acidic product (4·5 g) and fractional crystallization from aqueous methanol and chloroform–light petroleum (b.p. 40–60°) gave α-hydroxy-α-octylsebacic acid (1·75 g, 40%), m.p. 110–111°.

(b) *From 9-hydroxy-10-oxo- and 10-hydroxy-9-oxo-octadecanoic acids*

(i). The hydroxy-keto acids (1·03 g) and a finely powdered mixture of potassium and sodium hydroxides (1:1, 5 g) were heated at 230° for 30 min. The crude product (1·04 g) was isolated and shown (G.L.C. of methyl esters) to contain octanoic, nonanoic and azelaic acids in 1, 5 and 7% yields respectively. Crystallization of the crude product from chloroform–light petroleum (b.p. 40–60°) gave α-hydroxy-α-octylsebacic acid (0·49 g, 52%), m.p. and mixed m.p. 111°.

(ii). A solution of the hydroxy-keto acids (0·76 g) in 50% ethanolic potassium hydroxide (50 cc) was heated under reflux for 10 hr and then concentrated (to 20 cc) and diluted with water (50 cc). The solution was acidified with 2 N sulphuric acid, and steam distilled. From the distillate an acidic fraction (48 mg) was isolated which was shown (G.L.C. of methyl esters) to consist of octanoic (9%) and nonanoic acids (91%). The residual oil, involatile in steam, was separated, washed with hot water, dried (in ether) and crystallized from ethyl acetate to give α-hydroxy-α-octylsebacic acid (0·16 g), m.p. and mixed m.p. 111°. Azelaic acid (60 mg) was detected in the aqueous mother liquors.

(iii). A solution of the hydroxy-keto acids (1·7 g) in 10% potassium hydroxide (100 cc), and then water (20 cc), were added successively over 1½ hr to a stirred mixture of potassium hydroxide (5 g) and water (5 cc) in a copper vessel at 250°. The aqueous distillate was collected and extracted with ether. Evaporation of the extract left a residue (50 mg) which was shown by gas–liquid chromatography to contain nonanol (60%) and nonanal (40%). From the reaction vessel, α-hydroxy-α-octylsebacic acid (0·5 g), m.p. and mixed m.p. 111°, was isolated in the usual way.

(c) *From 9,10-dioxo-octadecanoic acid*

The diketo-acid (1·02 g), a finely powdered mixture of potassium and sodium hydroxides (1:1, 4 g), and a few drops of water, were heated at 160° for 15 min. The mixture was cooled, dissolved in water, and acidified. Steam distillation gave nonanoic acid (4%) which was identified by gas–liquid chromatography of its methyl ester. The residual oil, involatile in steam, was separated, washed with hot water, dried (in ether), and crystallized from chloroform–light petroleum (b.p. 40–60°) to give α-hydroxy-α-octylsebacic acid (0·75 g), m.p. and mixed m.p. 110–111°. Azelaic acid (4%) was detected in the aqueous mother liquors.

### *9-Oxoheptadecanoic Acid*

(a) *From erythro-9,10-dihydroxyoctadecanoic acid*

The dihydroxy acid (2·3 g) and potassium hydroxide (7 g) were heated at 260–270° for 1 hr. The mixture was cooled, dissolved in water, and the solution was acidified. Isolation of the product by

[16] H. Hunsdiecker, *Ber. Dtsch. Chem. Ges.* 77, 185 (1944).

extraction with light petroleum (b.p. 40–60°) and then with ether, and crystallization from light petroleum (b.p. 40–60°) or aqueous methanol, gave 9-oxoheptadecanoic acid (0·57 g), m.p. 79·5–80·5° (lit,[3] m.p. 78·5°) (Found: C, 72·4; H, 11·65. Calc. for $C_{17}H_{32}O_3$: C, 71·8; H, 11·3%). Esterification ($MeOH–H_2SO_4$) gave the methyl ester, m.p. 43–44° (lit,[3] m.p. 44°); $\nu_{max}$ 1715 (C=O) and 1735 $cm^{-1}$ ($CO_2Me$). A mixed m.p. with the ester of a specimen of 9-oxoheptadecanoic acid prepared by the method of Le Sueur and Withers[2] showed no depression.

(b) *From threo-9,10-dihydroxyoctadecanoic acid*

The dihydroxy acid (1·2 g) and potassium hydroxide (6 g) in water (10 cc) were heated in a nitrogen filled stainless steel autoclave at 340° for 2 hr. When the autoclave was opened, after it had been cooled, hydrogen was released. Isolation of the acidic product (1.05 g) in the usual way, and crystallization from aqueous methanol, gave 9-oxoheptadecanoic acid (0·14 g, 12%), m.p. and mixed m.p. 79–80°.

*Alkali fusion of* 10,11-*dihydroxyundecanoic acid*

The dihydroxy-acid (3.3 g) and potassium hydroxide (9 g) were heated at 300° for 1 hr. The mixture was cooled rapidly and dissolved in water (300 cc). The solution was acidified (evolution of $CO_2$) and the acidic product (3·1 g), m.p. 125–127° isolated with ether. Analysis (G.L.C. of methyl esters) revealed sebacic acid (ca. 95%), nonanoic acid (ca. 5%) and suberic acid (trace). One crystallization of a portion (0·56 g) of the crude product from water gave sebacic acid (0·50 g), m.p. and mixed m.p. 133–134°.

*Alkaline fission of* 9,10,12-*trihydroxyoctadecanoic acid*

(i) The trihydroxy-acid (1·28 g) and potassium hydroxide (5·2 g) were heated at 300° in a stream of nitrogen for 1 hr. The neutral product formed a fine cloud in the nitrogen stream from the reaction vessel, and collected partially in a cold (0°) trap inserted in the gas stream. Isolation with ether gave an oil (65 mg); analysis by gas–liquid chromatography on "Reoplex 400" (poly-ethylene adipate) at 130° indicated a composition 94% octan-2-ol and 6% octan-2-one; mixed chromatograms with authentic specimens showed no separation. Isolation of the acidic products in the usual way, and fractional crystallization of the dicarboxylic acid fraction from water, gave azelaic acid, m.p. and mixed m.p. 105–106°.

(ii) A solution of the trihydroxy-acid (6·4 g) in 30% potassium hydroxide (50 cc) was added with stirring over 90 min to potassium hydroxide (10 g) in a copper vessel at 300°. The steam distillate from the reaction vessel was condensed and the neutral product (0·8 g) isolated with ether; analysis by gas–liquid chromatography as described above indicated a composition 79% octan-2-ol and 21% octan-2-one; mixed chromatograms with authentic specimens showed no separation. After distillation, the mixture had $[\alpha]_D^{16} = +0{\cdot}13°$ in ethanol (active octan-2-ol has $[\alpha]_D^{17}$ 9·9°). Isolation of the acidic products gave mixtures similar to those from normal alkali fusions at 300° (Table 2).

*Alkali fusion of aleuritic acid*

The crude acid product from an alkali fusion of aleuritic acid at 250° for 1 hr was triturated with ether. The solid was collected, crystallized from ether–light petroleum (b.p. 40–60°), and then from aqueous methanol, giving *pentadecan-7-one-1,15-dioic acid* as plates, m.p. 103–104° (Found: C, 63·3; H, 9·1; O, 28·05. $C_{17}H_{28}O_5$ requires: C, 62·9; H, 9·15; O, 27·95%.) A mixed m.p. with aleuritic acid showed a marked depression. The methyl ester of the product had $\nu_{max}$ 1715 and 1735 $cm^{-1}$; the intensities of the bands were those expected for a keto-diester.

In another experiment fractional precipitation of the acidic product in ether with light petroleum (b.p. 40–60°) gave a solid. Crystallization from chloroform–methanol, and finally from water gave plates, m.p. 143–144° (Found: C, 60·75; H, 9·6; equiv., 147. $C_{16}H_{28}O_6$ require: C, 60·4; H, 9·5%; equiv. 153).

Elementary analyses were carried out in the micro-analytical laboratory (Miss J. Cuckney), and the spectral measurements in the spectroscopic laboratory (Mr. R. L. Erskine, Mrs. A. I. Boston) of this Department.

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# THE STRUCTURE OF DELPHININE

K. WIESNER, F. BICKELHAUPT, D. R. BABIN and M. GÖTZ
Organic Chemistry Laboratory, University of New Brunswick
Fredericton, N.B., Canada

(*Received* 2 *November* 1959)

**Abstract**—The complete structure XLIIIa has been proved for delphinine.

AMONG the alkaloids of the Aconitum–Delphinium–Garrya group, delphinine occupies a central position. It belongs to the most complicated representatives of this class and has been, since its isolation in 1819, repeatedly the target of structural studies in several laboratories.[1,2]

An additional stimulus to an attack on delphinine chemistry was provided by the similarity of many reactions of this alkaloid and those of the even more complex and extensively studied alkaloid, aconitine.[1] This similarity led us to believe that a solution of the delphinine problem might aid considerably in the task of unravelling the structure of aconitine.

We wish to describe in this Communication the details of our studies on delphinine which enabled us to propose the structure XLIII for this alkaloid.[3*]

The initial phase in the structure determination of delphinine was facilitated by the large amount of precise experimental work accumulated over a number of years by W. A. Jacobs *et al.*[4] Thus, Jacobs has clearly shown that delphinine has the empirical formula $C_{33}H_{45}O_9N$, and that it has six rings, a tertiary nitrogen carrying a N-methyl group, four methoxyls, a benzoxy, acetoxy and a tertiary hydroxy group. Jacobs has also performed a considerable amount of oxidative degradations.[4,5]

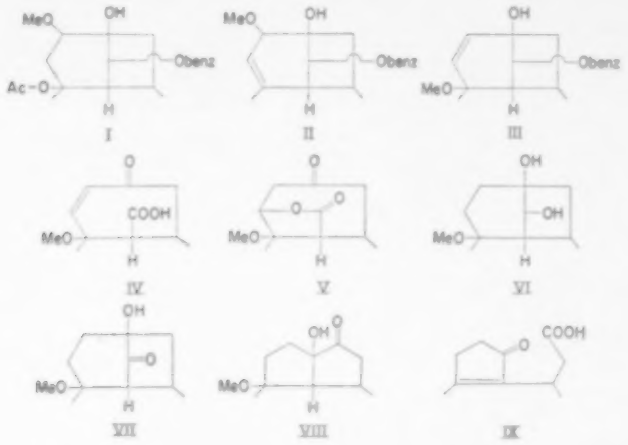
A careful analysis and repetition of this work, and our own additional experiments, enabled us first to deduce the partial structure I for delphinine.[6,7] The same partial structure also represents α-oxodelphinine ($C_{33}H_{43}O_{10}N$) which is a N-formyl compound.

Pyro-α-oxodelphinine ($C_{31}H_{39}O_8N$), which is obtainable from α-oxodelphinine by a pyrolytic loss of acetic acid, may be represented by the partial structure II, and the isomerization product of II, isopyro-α-oxodelphinine, is represented by the formula III. The isomerization II → III, which is carried out in methanolic hydrochloric acid,

* The structure XLIII was proposed for the first time as one of four possibilities for delphinine in a lecture by one of us (K. W.) at the Gordon Conference for steroids and related natural products, New Hampton, 30 July 1958. (See also ref. 7.)

[1] E. S. Stern, *The Aconitum and Delphinium Alkaloids* in: R. H. F. Manske and H. L. Holmes, *The Alkaloids, Chemistry and Physiology* Vol. IV, p. 275. Academic Press, New York (1954).
[2] K. Wiesner and Z. Valenta in L. Zechmeister, *Progress in the Chemistry of Organic Natural Products* Vol. XVI, p. 26. Springer, Wien (1958).
[3] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron Letters* No. 3, 11 (1959).
[4] For a summarizing reference, see: W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **78**, 3542 (1956).
[5] W. A. Jacobs and S. W. Pelletier, *J. Org. Chem.* **22**, 1428 (1957).
[6] K. Wiesner, F. Bickelhaupt and Z. Valenta, *Tetrahedron* **4**, 418 (1958).
[7] K. Wiesner, F. Bickelhaupt and D. R. Babin, *Experientia* **15**, 93 (1959).

is thus portrayed as an allylic rearrangement of a methoxyl. The transformations to be described in the sequel prove rigorously the correctness of our formulations.




We shall first focus our attention on the isopyro series and describe the structure proof of III. Hydrolysis of the benzoxy group in III gives the corresponding diol which Jacobs[5] oxidized to an $\alpha,\beta$-unsaturated keto acid represented by us as IV. Compound IV shows an ultraviolet maximum at 235 m$\mu$ ($\log \varepsilon = 3{\cdot}8$) and is easily isomerized into the $\gamma$-lactone V. Compound V shows two maxima in the carbonyl region of the infrared spectrum: 1706 cm$^{-1}$ (ketone) and 1783 cm$^{-1}$ ($\gamma$-lactone).

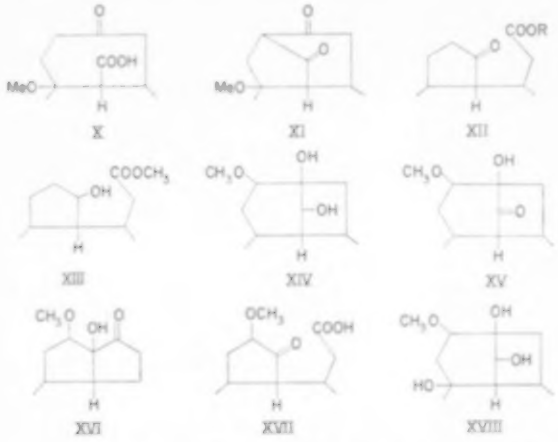
Hydrogenation of isopyro-$\alpha$-oxodelphinine III results in the saturation of the double bond and of the benzoyl group. The octahydro derivative may now be hydrolyzed to the corresponding diol, dihydro-$\alpha$-oxoisopyrodelphonine VI, and this last compound may be oxidized to the dihydro-$\alpha$-oxoisopyrodelphonone VII.[5] Compound VII shows a peak at 1754 cm$^{-1}$ in the carbonyl region of the infrared spectrum in agreement with a five-membered ring ketone.

Jacobs[5] has noticed that VII may be isomerized by treatment with alkali or on alumina to a more levorotatory isomer ($\Delta\alpha_D$ approx $= -110°$), which shows in the infrared spectrum a carbonyl band (1747 cm$^{-1}$) also in agreement with a five-membered ring ketone. Jacobs regarded this isomerization tentatively as an epimerization of an asymmetric centre adjacent to the carbonyl group. Such an explanation is, however, not admissible if we are to retain our partial structures, since both positions $\alpha$ to the keto group in VII are bridgeheads. We formulate the isomerization product of VII as VIII, and the isomerization is thus a simple acyloin rearrangement.

We have performed further experiments in order to test the formula VIII. Compound VIII takes up one mole of periodic acid and the expected seco keto acid eliminates spontaneously, on workup, a mole of methanol and gives a crystalline $\alpha,\beta$-unsaturated keto acid, $C_{23}H_{31}O_7N$, formulated as IX. Compound IX shows an ultraviolet spectrum ($\lambda_{max} = 250$ m$\mu$, $\log \varepsilon = 4$) which is shifted by approx 10-15 m$\mu$ to higher wavelength with respect to our expectations based on spectra of many known cyclopentenones. However, it seems that cyclopentenones are especially susceptible to spectral anomalies due to strain.

[5] W. A. Jacobs and Y. Sato, *J. Biol. Chem.* **180**, 479 (1949).

Thus, Fajkoš[9] has prepared in the steroid series a derivative in which an unsubstituted cyclopentenone chromophore absorbs at 235 m$\mu$. If we add to this value the expected increment for two substituents, we arrive at a value 257 m$\mu$ which is even higher than the one observed with compound IX. The infrared spectrum of IX is in agreement with the assigned constitution and shows a ketonic absorption at 1695 $cm^{-1}$ and a carboxyl at 1730 $cm^{-1}$.




Dihydro-α-oxoisopyrodelphonine VI may be converted by oxidation with chromic acid into a seco keto acid, $C_{24}H_{35}O_8N$, which has already been described by Jacobs[4] and was formulated by us as X.[7] The same author has shown[4] that compound X may be converted into a diketone, $C_{24}H_{33}O_7N$, by sublimation in high vacuo. We have formulated this last compound as XI. The infrared spectrum of XI shows ketonic carbonyl peaks at 1768 $cm^{-1}$ (five-membered) and 1727 $cm^{-1}$ (six-membered). If we take into account the strong dipole–dipole interaction of both keto groups due to the rigid structure of XI, we may expect a shift of both carbonyl peaks to higher wave numbers and the observed values for both carbonyls are thus in good agreement with the postulated structure.

As a further corroboration of the structure XI, we have found that this diketone gives quantitatively the seco acid IX by treatment with dilute aqueous alkali. Another way to obtain compound IX is the reflux of the oily methylester of X with methanolic sodium methoxide, followed by hydrolysis on workup. The intermediate in this reaction must be again the diketone XI. The significant point about this mode of formation of IX is the fact that the methylester of X does, as the first reaction, undergo a cyclization rather than an elimination of methanol. This fact can be explained by the assumption that a double bond obtained by a $\beta$-elimination of methanol in the structure X is probibited and suggests directly that the two points of attachment of the cycloheptane ring to the rest of the molecule are as indicated in formula X.

The exploration of the isopyro system was finally concluded by the following experiment. The seco acid IX was reduced by sodium amalgam in refluxing alcohol, the products esterified with diazomethane and separated by chromatography on alumina. One product was the oily ester XII (R = $CH_3$). This compound showed no

[9] J. Fajkoš, *Coll. Czech. Chem. Comm.* **23**, 1559 (1958).

hydroxyl band and a peak at 1739 $cm^{-1}$ (cyclopentanone and ester) in the infrared spectrum. Hydrolysis of this ester gave the corresponding acid XII (R = H). This compound also remained amorphous. It showed in the infrared spectrum a peak at 1731 $cm^{-1}$ (cyclopentanone) and 1710 $cm^{-1}$ (carboxyl). The fact that the peak at 1731 $cm^{-1}$ indeed belongs to the cyclopentanone follows not only from the spectrum of the corresponding ester XII ($R = CH_3$), but also from the finding that this peak is unchanged on salt formation.

The second product separated from the chromatogram was a crystalline hydroxy ester, $C_{24}H_{37}O_7N$, to which we ascribe the partial structure XIII. This compound was proved to be of special importance since it enabled us to correlate directly the isopyro series with a delphinine derivative which has not undergone the pyro-isopyro rearrangement (*vide infra*).

The transformations described up to this point prove conclusively the partial structure III for α-oxoisopyrodelphinine. The position of the benzoyl group in III follows from the fact that no derivative of III can be oxidized to a ketone before the removal of the benzoyl group.

We shall now turn to the description of a few experiments designed to show that α-oxopyrodelphinine II has the same skeletal structure as α-oxoisopyrodelphinine III, but differs from this last compound in the site of attachment on one methoxyl.*

Hydrogenation of II saturates the double bond and the benzoyl group, and by saponification of the resulting octahydro compound, dihydro-α-oxopyrodelphonine may be obtained.[4] We have formulated this compound as XIV.

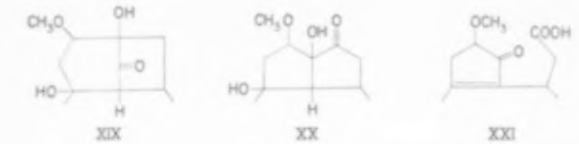
Compound XIV may now be subjected to a series of reactions which are completely analogous to the series VI → VII → VIII. Oxidation with chromium trioxide gives the ketone XV which may be isomerized with base to XVI.[5] The values of the ketonic carbonyl maxima in XV and XVI (1755 $cm^{-1}$, 1747 $cm^{-1}$) are quite similar to the corresponding values in compounds VII and VIII. Also the molecular rotation differences for the reactions VII → VIII and XV → XVI are approximately the same ($\Delta\alpha_D$ = approx −110°). The only difference between XVI and VIII, according to our formulation, is the site of attachment of one methoxy group. This is corroborated by the cleavage of both compounds with periodic acid.

As we have already discussed, the keto acid which is obtained in this manner from compound VIII eliminates spontaneously a mole of methanol and gives the cyclopentenone carboxylic acid IX. Compound XVI, on the other hand, is cleaved with periodic acid to the amorphous, but completely stable, keto acid XVII. The infrared spectrum of XVII shows a peak at 1744 $cm^{-1}$ (cyclopentanone) and 1709 $cm^{-1}$ (carboxyl). The fact that the 1744 $cm^{-1}$ peak indeed belongs to the cyclopentanone is easily demonstrated by esterification with diazomethane. The oily ester shows a single peak at 1743 $cm^{-1}$ which belongs both to the cyclopentanone and ester group.

The limited amount of data which we have collected on the pyro system II are thus in complete agreement with the structures proposed. The rigorous proof that no skeletal rearrangement has occurred in the change I → II → III was obtained by the study of α-oxodelphinine I. This compound was hydrolyzed to α-oxodelphonine XVIII, compound XVIII oxidized to α-oxodelphonone XIX (ketonic maximum in

* It should be pointed out that with the elucidation of the isopyro system as III the pyro-isopyro change must be a rearrangement and not merely a shift of a double bond as assumed by Jacobs.[4] The system III could be formed either by a skeletal rearrangement or an allylic rearrangement of the methoxyl.

IR 1751 $cm^{-1}$) and compound XIX finally isomerized by base to XX (ketonic maximum in IR 1747 $cm^{-1}$) according to the experimental procedures of Jacobs.[5] Again the rotation difference for the reaction XIX → XX ($\Delta\alpha_D$ approx $= -110°$) was approximately the same as the rotation difference for the rearrangement VII → VIII in the isopyro series.



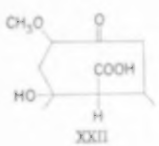

XIX



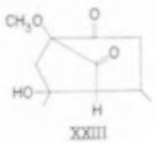

XX



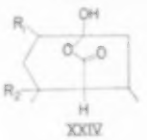

XXI



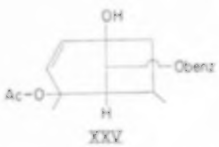

XXII



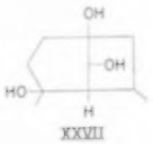

XXIII



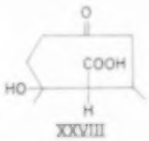

XXIV




XXV




XXVII




XXVIII

Compound XX took up one mole of periodic acid and yielded a crystalline acid, $C_{24}H_{33}O_8N$, which must have been formed by a spontaneous $\beta$-elimination of a hydroxyl from the original seco acid. We have formulated this compound as XXI. It shows an ultraviolet spectrum ($\lambda_{max}$ 257 m$\mu$, $\log \varepsilon = 4{\cdot}1$) very similar to the abnormal chromophore of compound IX. The small shift of the maximum of XXI to higher wavelength with respect to IX must be ascribed to an influence of the methoxyl in XXI which is absent in IX.

At this point we were able to correlate directly compound XXI with compound IX and thus to check all the partial structure assignments in the oxodelphinine and pyro-oxodelphinine series. Compound XXI was subjected to a sodium amalgam reduction in refluxing alcohol and the products were esterified with diazomethane and separated by chromatography on alumina. They were identified as the oily keto ester XII and crystalline hydroxy ester XIII which have been previously obtained by us in an analogous reduction experiment performed on compound IX (*vide supra*).

Jacobs has shown[4] that chromium trioxide oxidation of compound XIX gives a seco acid which we have formulated as XXII. We have also obtained this compound by treatment of compound XVIII with periodic acid, followed by neutralization and oxidation with permanganate.

In complete analogy to the transformations already discussed in the isopyro series, the methyl ester of XXII may be converted to the seco acid XXI by reflux with methanolic sodium methoxide followed by saponification on workup. Also in this case the diketone XXIII is presumably the intermediate. The same argument as in the isopyro series may be repeated in the present case; i.e. the transformation XXII → XXI is made possible by the remarkable reluctance of the ester of compound XXII to eliminate the $\beta$-hydroxyl. The simplest explanation of this situation is again the assumption that the resulting double bond would be impossibly strained due to the

mode of attachment of the cycloheptane system XXII to the rest of the molecule.

The infrared spectra of the seco acids X (1736 $cm^{-1}$ $\delta$-lactone, sharp hydroxyl peak at 3300 $cm^{-1}$) and XXII (1730 $cm^{-1}$ $\delta$-lactone, 3500 $cm^{-1}$ hydroxyl) deserve a brief remark. It appears that the keto acid forms X and XXII are in equilibrium with the pseudoacid forms XXIV ($R_1 = H$, $R_2 = OCH_3$; $R_1 = OCH_3$, $R_2 = OH$ respectively) and that these latter predominate in chloroform solution. On the other hand, the esters of X (1750 $cm^{-1}$ ester, 1703 $cm^{-1}$ ketone) and XXII (1741 $cm^{-1}$ ester, 1715 $cm^{-1}$ ketone, 3500 $cm^{-1}$ hydroxyl) are normal keto esters.

From all the transformations discussed up to now, the partial structures I, II and III for α-oxodelphinine, pyro-α-oxodelphinine and isopyro-α-oxodelphinine follow rigorously. Consequently, it is clear that the pyro-isopyro change must, in fact, be an allylic rearrangement of a methoxyl. However, before proceeding with the elucidation of the remaining part of the delphinine molecule we have decided to subject this conclusion to a direct test. We have isomerized α-oxopyrodelphinine II in radioactive methanol, and as expected radioactivity corresponding to one mole of methanol was incorporated into the resulting α-oxoisopyrodelphinine III.

We have also found that it is not possible to prepare III in any medium other than methanol. Thus, for instance, α-oxopyrodelphinine II, when treated with *p*-toluenesulfonic acid in glacial acetic acid, exchanges quantitatively a methoxyl for an acetoxy group and yields a compound, $C_{32}H_{39}O_9N$, formulated as XXV. Hydrogenation of XXV gives an octahydrocderivative XXVI which may be saponified to the triol $C_{23}H_{35}O_7N$, XXVII. Compound XXVII was then converted to the crystalline acid IX by oxidation with chromium trioxide, esterification of the resulting uncharacterized seco acid XXVIII to the corresponding methyl ester and treatment of this last compound by refluxing methanolic sodium methoxide followed by hydrolysis. It is clear that this new mode of formation of IX is entirely analogous to the route VI → X → IX.

The series of experiments just described proves directly:

(a) that the pyro system rearranges to the isopyro system with a simultaneous exchange of a methoxyl for a nucleophylic solvent molecule,

(b) that, as postulated by our scheme, the group which replaces a methoxyl in the pyro-isopyro rearrangement is the one which ultimately eliminates in the formation of the unsaturated seco acid IX.

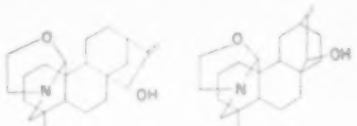
After the completion of all these studies, it was clear that there is no doubt left about the correctness of the partial formula I for delphinine, and that the stage is set for an attempt to extend it into a complete structure.

Having considered the problem carefully, we have decided to abandon the systematic approach pursued until now and to set up a hypothesis for the complete structure, which could be confronted with the mass of scattered data in the literature,[1,3] as well as with new experiments designed to test it. Fortunately, we were in possession of a certain amount of purely chemical information which has enabled us to write down readily two very plausible delphinine structures.

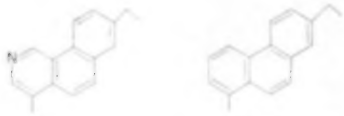
In 1953 we deduced the structures of the first two alkaloids belonging to the aconite–garrya class.[1,10] They were the alkaloids, veatchine XXIX and atisine XXX. The key evidence which gave the idea for the proposal of the two diterpenoid alkaloid skeleta was the formation of the compounds XXXI and XXXII on dehydrogenation of veatchine. Similarly, the dehydrogenation of atisine gave the phenanthrene XXXIV

[10] K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954).

and a base which we, at that time, postulated to be XXXIII. Later the structure of the atisine dehydrogenation base XXXIII was confirmed by synthesis.[11]



XXIX XXX



XXXI XXXII

XXXIII XXXIV

This reasoning by which the skeleton of a diterpenoid alkaloid is revealed from the structures of two "overlapping" dehydrogenation products is applicable also to hexacyclic representatives of this group. We have postulated the structure XXXV[12] ($R_1$ = O=; $R_2$ = $CH_2$=) for the alkaloid songorine. This compound yields as

XXXV XXXVI

XXXIX (R = H or $CH_3$) XL

XXXVII XXXVIII

[11] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.* **80**, 2588 (1958).
[12] K. Wiesner, Shô Itô and Z. Valenta, *Experientia* **14**, 167 (1958).

characteristic dehydrogenation products the veatchine azaphenanthrene XXXI[12] and the dimethyl ethyl phenanthrene XXXVI.[13]

We have naturally attempted a dehydrogenation of delphinine in order to ascertain whether the typical dehydrogenation products of the simpler aconite alkaloids can be isolated also in this case.

While it was possible to demonstrate spectroscopically traces of phenanthrenes and azaphenanthrenes on chromatography of the dehydrogenation mixture, no compound of this type was isolated in pure form. However we have obtained a good indication of the skeletal system of delphinine by the study of the alkaloid neoline ($C_{24}H_{39}O_6N$) which accompanies aconitine in Aconitum napellus. The parallelism of many transformations of neoline and delphinine, has convinced us that the two alkaloids must possess the same skeleton.[14] Especially the presence in neoline of the delphinine (1-2-3) bicyclo-octane system I in which the tertiary hydroxyl was missing and the two ester groups were replaced by hydroxyls was assured.

The dehydrogenation of neoline has now, possibly because of the lesser substitution of this alkaloid, yielded positive results.[14] It gave the azaphenanthrene XXXVII and a phenanthrene XXXVIII which had the empirical composition $C_{19}H_{20}$ or $C_{18}H_{18}$.

In the course of our studies on songorine (XXXV, $R_1 = O{=}$; $R_2 = CH_2{=}$) and napelline (XXXV, $R_1 = -OH$; $R_2 = CH_2{=}$) which accompany neoline in the mother liquors of Aconitum napellus, Maudgal has performed a dehydrogenation of dihydronapelline (XXXV, $R_1 = OH$; $R_2 = -CH_3$). He was able to isolate from the dehydrogenation mixture a phenanthrene $C_{19}H_{20}$ or $C_{18}H_{18}$ which was later recognized as identical with XXXVIII from neoline. This finding has, of course, a profound significance for the tentative deduction of a possible neoline and delphinine skeleton, since dihydronapelline is a compound of known structure.

A further point to be emphasized is that the connection between napelline and neoline, established through the common dehydrogenation product XXXVIII, extends clearly to the earliest representative of the garrya–aconite class, veatchine XXIX. As already stated, veatchine and napelline yield by dehydrogenation the same azaphenanthrene XXXI.

It is clear that delphinine and neoline must possess a skeleton which is capable of yielding the same dehydrogenation products as XXXV ($R_1 = -OH$; $R_2 = -CH_3$). Both neoline and XXXV ($R_1 = -OH$; $R_2 = -CH_3$) may of course be assumed to dehydrogenante with or without a plausible rearrangement.

A further limitation imposed on the neoline skeleton is the requirement that it must accommodate the properly substituted 1,2,3-bicyclo-octane system and have an oxygen function correctly placed for any postulated rearrangement.

It is very easy to see that there are two schemes that satisfy these requirements. If neoline is XL, it may rearrange to XXXIX (R = H) and this intermediate may give the dehydrogenation products XXXVII and XXXVIII.

The same dehydrogenation phenanthrene XXXVIII may be obtained from XXXV ($R_1 = -OH$; $R_2 = -CH_3$) via a rearrangement to XXXIX ($R = -CH_3$) in a manner indicated by the arrows in formula XXXV.

[13] A. D. Kuzovkov, *Zh. Obshch. Khim.* **28**, 2283 (1958); E. Ochiai, T. Okamoto, S. Sakai, T. Sugasawa and T. Onouchi, In press.

[14] K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Babin, F. Bickelhaupt, J. Kallos and T. Bogri, *Tetrahedron Letters* No. 3, 17 (1960).

The second possibility is the skeleton XLI for neoline. This system may rearrange, as indicated, to XLII. Finally, this last intermediate may yield on dehydrogenation the azaphenanthrene XXXVII and the phenanthrene XXXVIII, which may also be obtained from XXXV by a dehydrogenation without rearrangement.

Both XL and XLI contain the 1,2,3-bicyclo-octane system attached and substituted in a manner compatible with the rigorously established partial structure of delphinine and neoline.

For these reasons we have decided to consider seriously XL and XLI as very plausible working hypotheses for the complete skeletons of delphinine and neoline.

The skeleton XL has of course an important precedent. The brilliant crystallographer, Przybylska, solved the structure of lycoctonine which was shown by her to be based on this system.[15] It was then recognized independently in our laboratory[16] and by Cookson[17] that the system XL may arise by a simple rearrangement, bridging, and loss of a methyl group from the atisine skeleton.

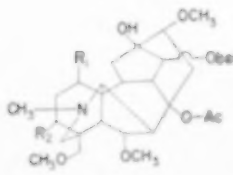
The preceding arguments show that one can readily deduce the skeleton XL by purely chemical reasoning.

We shall now turn our attention to the disposition of the remaining functional groups in the skeletons XL or XLI, as well as to the proof that one of these structures is really correct.

The disposition of functional groups in the 1,2,3-bicyclo-octane system of XL or XLI follows clearly from the partial structure I. The remaining functions were distributed in such a manner as to accommodate experimental work already available in the literature.[18] This led to the four structures for delphinine XLIII (a and b) and XLIV (a and b). Most of the reactions discussed in the sequel can be fitted equally well into all four structures. Since, however, the structure XLIIIa was ultimately

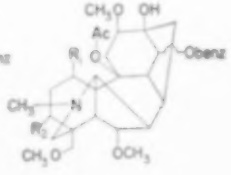
XLI

XLII




XLIII

(a) $R_1 = OCH_3$, $R_2 = H$
or
(b) $R_1 = H$, $R_2 = OCH_3$




XLIV

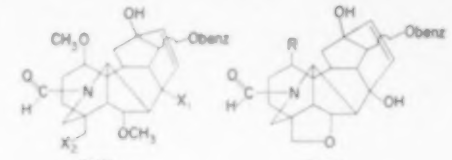
(a) $R_1 = OCH_3$, $R_2 = H$
(b) $R_1 = H$, $R_2 = OCH_3$

[15] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[16] Z. Valenta and K. Wiesner, *Chem. & Ind.* 354 (1956).
[17] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 3121 (1956).
[18] W. A. Jacobs and S. W. Pelletier, *J. Amer. Chem. Soc.* **76**, 161 (1954).

shown to be correct, we shall use only this particular representation in order to conserve space.

Jacobs[18] has shown that in α-oxoisopyrodelphinine a tertiary and a primary methoxyl are readily displaced by chlorine. The resulting dichloro derivative may be converted by methanol back into α-oxoisopyrodelphinine, or by water into the corresponding dihydroxy derivative. This last compound may be oxidized into a hydroxy acid in which the carboxyl seems to be tertiary.

It is clear that the tertiary methoxyl displaced by chlorine must be the one engaged in the pyro-isopyro rearrangement. The fact that the same dichloride is obtained both from pyro- and isopyro-α-oxodelphinine is sufficient proof of this assumption. We may, consequently, formulate the dichloride as XLVa and the hydroxy acid as XLVb.



XLV

(a) $X_1, X_2 = Cl$

(b) $X_1 = OH$, $X_2 =$

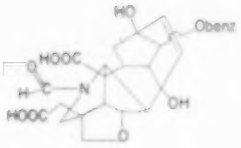
(c) $X_1, X_2 = OCD_3$



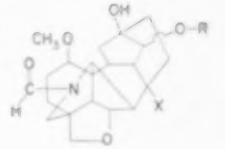
XLVI

(a) R = –OH

(b) R = =O



XLVII



XLVIII

(a) R = hexahydrobenzoyl, X = $-OCH_3$

(b) R = hexahydrobenzoyl, X = $-OCD_3$

Jacobs[18] has further shown that treatment of α-oxoisopyrodelphinine with aqueous zinc chloride will result in the replacement of two methoxyls by hydroxy groups and the remaining two methoxyls are lost with the simultaneous formation of a cyclic ether. We formulate the product of this complete demethoxylation as XLVIa. Compound XLVIa has been oxidized by Jacobs to the corresponding ketone formulated here as XLVIb. The infrared absorption of the keto group in XLVIb (1712 $cm^{-1}$) is in agreement with a keto group in a six-membered ring.[4] A more vigorous oxidation of XLVIb by chromium trioxide gave [18] a dicarboxylic acid formulated here as XLVII. Compound XLVII was esterified and one of the two ester groups in the resulting dimethylester was found to be resistant to saponification.

We shall now consider the identity of the two methoxyls which are engaged in the formation of the cyclic ether. Already Jacobs[18] has correctly deduced that one of them is the primary methoxyl which may be displaced by chlorine. This follows clearly from the fact that compound XLVIa (according to the results of its oxidation to XLVIb and XVLII) does not possess a primary hydroxyl. Jacobs has further postulated[4] that the second methoxyl engaged in the cyclic ether formation is identical with the

tertiary methoxyl displaced by chlorine in the formation of the dichloride XLVa. However, a careful analysis of the data shows that this assumption has no experimental basis and, in fact, is quite unlikely. Thus, according to our structure XLVIa, a new methoxyl which is not identical with either of the two methoxyls displaced by chlorine forms the second terminus of the cyclic ether.

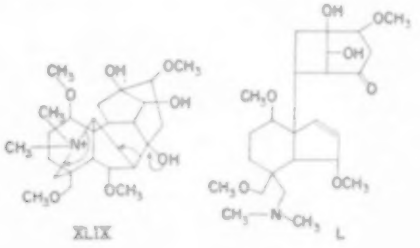
The key to the experimental decision of this point was a compound described by Jacobs[18] and formulated by us as XLVIIIa. It may be obtained by treatment of octahydro-α-oxoisopyrodelphinine with aqueous zinc chloride and it contains the cyclic ether with retention of the remaining two methoxyls.

We have prepared hexadeutero-α-oxoisopyrodelphinine XLVc by treatment of the dichloride XLVa with $CD_3OH$. The octahydroderivative of XLVc was then converted to XLVIIIb which still contained one deuterated methoxyl. This shows conclusively that as predicted by our scheme one of the two methoxyls which may be displaced by chlorine does not participate in the cyclic ether formation. All the deuterated delphinine derivatives were practically indistinguishable in properties from their only hydrogen containing analogs, but they gave correct deuterium analyses and showed deuterium bands in the infrared spectrum (see experimental part).

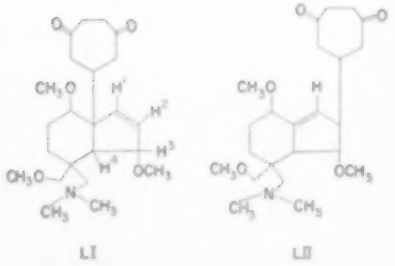
All the evidence we have discussed up to now has convinced us that one of the two delphinine structures XLIII or XLIV is correct, however, none of the data enabled us to differentiate between them rigorously.

A rigorous decision between XLIII and XLIV, which at the same time provided us with a dramatic corroboration of XLIII, was achieved by the clarification of the Hofmann degradation of delphonine. A successful Hofmann degradation of this compound has been reported by Schneider.[19] As it is clear that this finding cannot be explained by the structures XLIII or XLIV in a simple manner, we have decided to reinvestigate it.

Delphonine formed a crystalline methiodide XLIX which melted at 208–211°. The



XLIX L



LI LII

[19] W. Schneider, *Archiv. Pharm.* **283**, 86, 281 (1950).

methiodide was converted into a methohydroxide on a column of Amberlite IRA-400, and the methohydroxide was heated with 10 per cent aqueous sodium hydroxide until most of the water evaporated. From the resulting products a crystalline base, $C_{23}H_{37}O_5N$, was isolated by extensive countercurrent distribution. The infrared spectrum of this compound shows a strong ketonic peak at 1707 $cm^{-1}$ and no peak in the hydroxyl region. The analysis indicated three methoxyls, and the presence of two keto groups was corroborated by the preparation of a bis-2, 4-dinitrophenylhydrazone.

We ascribe to this product the structure LI. It can be formed by an initial 1-3 cleavage as indicated by the arrows in formula XLIX. The product of this reaction, L, may now be converted to LI by a reverse aldol reaction, $\beta$-elimination of a methoxyl and vinilogous $\beta$-keto aldehyde cleavage. The order in which these last three steps occur can, of course, not be specified.

In this way the supposed Hofmann degradation of delphinine is explained in terms of an extensive base catalysed breakdown of the molecule and the "methine" of Schneider[19] may be conceivably identical with our compound LI.

The properties of LI discussed so far do not rule out, of course, the structure XLIV for delphinine. This last formula has all the required relationships of functional groups to undergo a similar degradation to LII. However, it was possible to decide between the two structures LI and LII for our "Hofmann product" on the basis of the NMR spectrum.

The "Hofmann product" shows in the NMR spectrum (toluene scale) a doublet with an area 1H at 1014, 1019 cps which we assign to $H_2$ split by the adjacent $H_1$. Both peaks of this doublet show a further slight splitting of approximately 1·1 cps which we ascribe to the adjacent hydrogen $H_3$. A further doublet at 1029, 1034 cps, which has the same splitting as the first one and an area of 1H, may be ascribed to $H_1$ split by the adjacent hydrogen $H_2$. It is characteristic that this second doublet (1029, 1034 cps) is a clean doublet without the secondary splitting.

A third doublet with an area 1H is located at 1091, 1096·5 cps and ascribed to $H_3$ unshielded by the methoxyl and split by the adjacent hydrogen $H_4$. Both peaks of this doublet again show secondary splitting of 1·1 cps caused by the adjacent hydrogen $H_2$. It is clear that this situation is incompatible with the formula LII which could show in the NMR spectrum only one doublet in the region of vinylic hydrogens. Consequently, we may assign the structure LI to our "Hofmann product", and structure XLIII to delphinine itself.[3] The last problem which had to be solved was the decision between the two possible locations of the ring A methoxyl in delphinine (i.e. the structures XLIII a and b).

An analogous uncertainty remained also in the complete structure of aconitine proposed some time ago.[20] In aconitine, ring A was known to be substituted by a methoxyl and hydroxyl in the 1 and 3 position, but no conclusive argument was available whether the locations of these substituents should not be exchanged. This problem was recently solved in aconitine by chemical studies[21] and also X-ray crystallography.[22] Both methods in agreement assigned the position 1 to the methoxyl and 3 to the hydroxy group. We have recently been able to convert aconitine and delphinine into an identical derivative. This correlation shows that the ring A methoxyl

[20] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters* No. 2, 15 (1959).
[21] G. Büchi, private communication.
[22] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1116 (1959).

of delphinine is located in the same position as the corresponding substituent of aconitine, and that consequently the structure XLIIIa is the correct representation of delphinine.

The correlation of aconitine and delphine was reported by a preliminary letter[23] and the details of this work will be described in a complete article on aconitine chemistry.

## EXPERIMENTAL

*Secoacid* IX

(a) *From ketol* VIII. Dihydro-α-oxoisopyrodelphonone VII was prepared and isomerized to VIII according to the procedure given by Jacobs.[5] The ketol VIII (104 mg) was dissolved in 10 ml ethanol and treated for 5 hr with a solution of 150 mg periodic acid in 10 ml water. The alcohol was then evaporated *in vacuo* at room temp and the remaining aqueous phase was extracted exhaustively with chloroform. The acidic fraction from this chloroform extract was separated in the usual way and crystallized from benzene–ether. The yield was 23 mg and the final melting point 138°. This material showed no m.p. depression with a sample of IX described in the subsequent experiment. Both samples also showed superimposable infrared spectra.

(b) *From secoacid* X. The secoacid X was prepared according to Jacobs[4] and remained amorphous. It was purified by chromatography on silicic acid and converted into the oily methyl ester with diazomethane. This last compound (117 mg) was dissolved in 10 ml absolute methanol and refluxed with a solution of 0·6 g sodium in 30 ml absolute methanol. After 2 hr an equal volume of water was added and the methanol swirled off *in vacuo*. The alkaline solution was exhaustively extracted with chloroform, acidified and extracted again. The yield of acidic material was 90 mg and it was recrystallized from benzene–ether to a constant m.p., 138°. (Found: C, 61·38; H, 7·24; N, 2·92; $OCH_3$, 19·99. Calc. for $C_{23}H_{31}O_7N \cdot H_2O$: C, 61·18; H, 7·37; N, 3·10; $3OCH_3$, 20·62%). Infrared spectrum, (KBr) 1730, 1695, 1668, 1641 $cm^{-1}$. Ultraviolet spectrum (ethanol) $\lambda_{max}$ 250 mμ, log $\varepsilon = 4·0$.

(c) *From diketone* XI. The diketone XI was prepared by sublimation of the secoacid X according to Jacobs.[4] The diketone (31 mg) dissolved in 5 ml ethanol and 20 ml 0·01 M aqueous sodium hydroxide was added. After 30 min at room temp the solution was acidified and extracted with chloroform. The yield (36 mg) of foam which crystallized from benzene–ether and was recrystallized to a constant m.p., 138°. This material has been found to be identical with compound IX obtained in experiment (b) by mixed m.p., ultraviolet and infrared spectrum.

*Reduction of secoacid* IX

Compound IX (50 mg was refluxed in 10 ml ethanol with 500 mg 8% sodium amalgam for 12 hr. The solution was decanted and the amalgam washed with water. The solution and washing were combined and the ethanol evaporated *in vacuo*. The acidic fraction was separated in the usual manner and yielded 50 mg of material. The acids were esterified with diazomethane and the esters chromatographed on 5 g alumina. The ester XII (R = $CH_3$, 19 mg) was eluted with 0·5% methanol in benzene. The hydroxy ester XIII (22 mg) was eluted in a subsequent fraction with 1% methanol in benzene. Ester XII (R = $CH_3$) infrared spectrum ($CCl_4$) 1739, 1672 $cm^{-1}$.

The acid XII (R = H) was prepared by saponification of the ester with 5% aqueous methanolic potassium hydroxide under reflux, followed by a separation of the acidic material in the usual manner. Infrared spectrum (acid), (KBr) 1730, 1713, 1660 $cm^{-1}$. Infrared spectrum (sodium salt), (KBr) 1730, 1659, 1580 $cm^{-1}$.

The hydroxy ester XIII was recrystallized to a constant m.p. of 197° from benzene–ether. (Found: C, 63·99, 63·74; H, 8·16, 8·01; $OCH_3$, 27·22. Calc. for $C_{24}H_{37}O_7N$: C, 63·83; H, 8·26; $4OCH_3$, 27·48%). Infrared spectrum (KBr) 1729, 1653 $cm^{-1}$.

The sample was found to be identical by mixed m.p. and infrared spectrum with the ester XIII prepared by reduction of the acid XXI (*vide infra*).

*Secoacid* XVII

The ketone XVI was prepared according to Jacobs[5] by isomerization of dihydro-α-oxopyrodelphonone XV. Compound XVI (20 mg) was dissolved in 5 ml ethanol and a solution of 42 mg

[23] K. Wiesner, D. L. Simmons and L. R. Fowler, *Tetrahedron Letters* No. 18, 1 (1959).

periodic acid in 4 ml water was added. After 2 hr the reaction mixture was diluted with an equal volume of water and the ethanol evaporated *in vacuo* at room temp. The solution was then exhaustively extracted with chloroform and the acidic fraction from the chloroform extract was separated in the usual manner. It yielded 14 mg of colorless glass. This material did not have any high extinction ultraviolet chromophore and it did not develop such a chromophore on treatment with acid or base on the steam bath. Infrared spectrum ($CHCl_3$) 1744, 1709, 1660 $cm^{-1}$. The acid was esterified with diazomethane to the oily ester. Infrared spectrum of ester, ($CCl_4$) 1743, 1678 $cm^{-1}$.

*Secoacid* XXI

(a) *From ketol* XX. α-Oxodelphonone XIX was prepared and isomerized to XX according to the prescription of Jacobs.[8] Compound XX (70 mg) was dissolved in 3 ml water and 10 ml of a 1% aqueous solution of periodic acid was added to it. After 19 hr the aqueous layer was exhaustively extracted with chloroform and the acidic fraction from the chloroform extract was separated in the usual manner. The yield of acid was 57 mg and it was recrystallized to a constant m.p. of 187° from ethanol. (Found: C, 61·70; H, 7·58; O, 28·02; N, 3·00. Calc. for $C_{24}H_{33}O_8N \cdot \frac{1}{2}C_2H_5OH$): C, 61·70; H, 7·46; O, 27·99; N, 2·88%). Infrared spectrum, (KBr) 1731, 1709, 1644, 1628 $cm^{-1}$. Ultraviolet spectrum (ethanol), $\lambda_{max} = 257$ mμ, log $\varepsilon = 4.07$.

Esterification of acid XXI with diazomethane gave the oily methyl ester. Infrared spectrum ($CCl_4$), no OH band; 1742, 1710, 1677, 1655 $cm^{-1}$.

(b) *From secoacid* XXII. The secoacid XXII was obtained according to Jacobs[8] as the acidic by-product in the oxidation of α-oxodelphonine XVIII to α-oxodelphonone XIX with chromic acid. Compound XXII (280 mg) was esterified with ethereal diazomethane to the oily methyl ester. This last compound was dissolved in a solution of 0·6 g sodium in 50 ml absolute methanol and refluxed for 2 hr. The methanol was then evaporated to a small volume *in vacuo* at room temp and water added. From the aqueous solution the acidic material was isolated in the usual manner. The yield of acid was 156 mg and it was esterified with diazomethane and chromatographed on 6 g alumina. Chloroform eluted 50 mg of an oil which was, according to its infrared spectrum, identical with the methylester of compound XXI prepared in the previous experiment. It was saponified with 5% methanolic sodium hydroxide in a quantitative yield to the acid which was recrystallized from ethanol to the constant m.p. of 187°. This material gave no m.p. depression with compound XXI prepared in experiment (a), and the two samples showed identical ultraviolet and infrared spectra.

*Sodium amalgam reduction of the secoacid* XXI

The secoacid XXI (108 mg) was dissolved in 29 ml ethanol, 2·84 g 8% sodium amalgam was added and the suspension was heated under reflux for 7 hr. After this period the solution was decanted and worked up exactly as in the reduction of the secoacid IX. The yield of acidic material was 92 mg and it was esterified with ethereal diazomethane. The esters were chromatographed on 10 g alumina. An oily fraction of 24 mg was eluted with 0·5% methanol in benzene. The infrared spectrum of this material was identical with the corresponding spectrum of compound XII (R = $CH_3$) previously obtained by the analogous reduction of the secoacid IX.

On further elution of the chromatograph with 1% methanol in benzene, 50 mg of oil was eluted. This material crystallized from benzene and after recrystallization from the same solvent reached the constant m.p. of 197°. The substance proved to be identical by mixed m.p. and infrared spectrum with the ester XIII previously obtained by a reduction of the secoacid IX.

*Acetoxyisopyro-α-oxodelphinine* XXV

To 2·03 g pyro-α-oxodelphinine dissolved in 53 ml glacial acetic acid was added a solution of 810 mg *p*-toluenesulphonic acid in 30 ml glacial acetic acid. After being allowed to stand for 15 min at room temp the mixture was heated to 60–70° for 30 min. At the end of this period 200 ml water were added and the solution extracted exhaustively with chloroform. The yield of material thus obtained was 1·91 g and it was recrystallized from chloroform–ethanol to a constant m.p. of 305°. (Found: C, 66·35; H, 6·75; $OCH_3$, 15·51. Saponification equivalent 271. Calc. for $C_{32}H_{39}O_9N$: C, 66·07; H, 6·76; $3OCH_3$, 16·00%. Saponification equivalent 290·8). Infrared spectrum, (KBr) 1732, 1714, 1643 $cm^{-1}$.

*Octahydroacetoxyisopyro-α-oxodelphinine*

Compound XXV (1·53 g) was hydrogenated in 50 ml glacial acetic acid with 200 mg prehydrogenated platinum oxide. The uptake of four molecules of hydrogen was completed in 9 hr. The solution was then evaporated to dryness and the hydrogenation product recrystallized from chloroform–ether to a constant m.p. of 229°. The yield of once recrystallized material was 1·42 g. (Found: C, 65·45; H, 7·97; $OCH_3$, 15·96. Calc. for $C_{22}H_{47}O_9N$: C, 65·17; H, 8·03; $3OCH_3$, 15·82%). Infrared spectrum, (KBr) 1735, 1648 $cm^{-1}$.

*Desmethoxy-α-oxodelphonine* XXVII

The above octahydro compound (1·11 g) was dissolved in 32 ml methanol and 8 ml of 10% aqueous sodium hydroxide was added. The solution was heated under reflux for 2 hr. After this time the methanol was evaporated *in vacuo* and the aqueous layer extracted with chloroform. The chloroform extract was evaporated to dryness and the residue recrystallized from methanol to a constant m.p. of 239°. The yield after one crystallization was 678 mg. (Found: C, 63·29; H, 8·04; $OCH_3$, 20·87. Calc. for $C_{23}H_{35}O_7N$: C, 63·14; H, 8·06; $3OCH_3$, 21·28%). Infrared spectrum, (KBr) 1648 $cm^{-1}$.

*The secoacid* XXVIII

The compound XXVII (504 mg) was dissolved in 30 ml glacial acetic acid and 0·5 ml of a 10% aqueous solution of chromic acid was added dropwise over a period of 15 min with stirring. After 30 min, 2 hr and 6 hr additional 0·5 ml portions of the same chromic acid solution were added in the same manner. After the last addition the solution was allowed to stand at room temp for 20 hr. At the end of this period the mixture was diluted with 50 ml water and the acidic oxidation product was separated in the usual way, using chloroform for the extractions. The yield was 108 mg of a white foamy acid which did not crystallize. The infrared spectrum of this material was typical of the seven-membered secoacids of this series and was compatible with the formula XXIV ($R_1$ = H, $R_2$ = OH) rather than XXVIII. Infrared spectrum, ($CHCl_3$) 3600, 3400 (hydroxyl), 1725 (lactone), 1660 $cm^{-1}$ (amide).

*Secoacid* IX

The above acid (108 mg) was esterified with ethereal diazomethane. The oily ester was dissolved in 10 ml absolute methanol and added to a solution of 194 mg sodium in 68 ml of the same solvent. The mixture was heated under reflux for 2 hr. At the end of this period 60 ml water was added and the methanol evaporated *in vacuo*. The alkaline aqueous solution was extracted with chloroform, acidified and extracted again. The residue of the second chloroform extract was recrystallized from benzene–ether to give 32 mg of the secoacid IX. After several crystallizations the substance melted at 138° and showed no depression of m.p. on admixture of a sample of the secoacid IX prepared from α-oxoisopyrodelphinine. Also the ultraviolet and infrared spectra of both samples were identical.

*Pyro-isopyro rearrangement in labelled methanol*

(a) *In deuterated methanol.* α-Oxopyrodelphinine (193 mg) was heated to 60° in 6 ml deuterated methanol ($CD_3OH$) and 0·35 ml conc hydrochloric acid for 15 min. The crystalline product was then filtered off, washed with ordinary methanol and recrystallized from chloroform–ether and chloroform–ordinary methanol until it reached a constant m.p. of 287°. The infrared spectrum of this material was superimposable with the spectrum of α-oxoisopyrodelphinine except that the deuterated material showed additional bands at 2245, 2215 and 2070 $cm^{-1}$, not present in α-oxoisopyrodelphinine. (Found: 6·44 atom per cent XSS D. Calc. for $C_{21}H_{26}D_3O_9N$: 7·69 atom per cent XSS D.)

(b) *In $C^{14}$-methanol.* α-Oxopyrodelphinine (408 mg) was dissolved in 8·5 ml $C^{14}$-methanol (molar activity—$2·0 \times 10^{-3}$ mc/mole). After an addition of 0·5 ml 38% hydrochloric acid the solution was kept at 60° for 10 min. The crystalline labelled α-oxoisopyrodelphinine was filtered off and recrystallized from chloroform–ether and chloroform–ordinary methanol to a constant m.p. of 287°. The yield was 181 mg. The counting of the labelled sample was done as $BaCO_3$ and compared with a calibration curve constructed with samples of $BaCO_3$ of known activity. The combustion was performed according to the Van Slyke method.[24]

[24] M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. E. Yankwich, *Isotopic Carbon* p. 92. Wiley, New York (1949).

In three separate combustions the labelled α-oxoisopyrodelphinine was found to have a molar activity 106, 102 and 99% of the molar activity of the labelled methanol used for the rearrangement. This corresponds to the incorporation of exactly one mole of methanol.

*Dichloro-α-oxoisopyrodelphinine* XLVa

This compound was prepared according to Jacobs[15] in quantitative yield. α-Oxopyrodelphinine was dissolved in absolute methanol saturated with hydrochloric acid at 0°. The reaction mixture was allowed to stand overnight at room temp. The highly insoluble compound XLVa was filtered off and recrystallized from chloroform–ether. It started decomposing without melting at about 270°. (Found: C, 61·79; H, 5·95; Cl, 13·42; $OCH_3$, 12·10. Calc. for $C_{29}H_{32}O_6NCl_2$: C, 61·90; H, 5·92; Cl, 12·61; $2OCH_3$, 11·03%.)

*Hexadeutero-α-oxoisopyrodelphinine* XLVc

A suspension of 756 mg of compound XLVa and 1 g silver nitrate in 25 ml $CD_3OH$ was heated under reflux for 18 hr. The solution was then evaporated to dryness and the residue was extracted with chloroform. After one crystallization from chloroform–ether 500 mg labelled α-oxoisopyrodelphinine XLVc was obtained. The compound reached after several crystallizations, a constant m.p. of 285° and gave no m.p. depression with α-oxoisopyrodelphinine. The infrared spectra of both samples were identical except for the presence in the spectrum of the labelled compound of additional bands at 2050, 2180 and 2245 $cm^{-1}$. (Found: 13·0 atom per cent XSS D. Calc. for $C_{31}H_{33}D_6O_6N$: 15·4 atom per cent XSS D.)

*Hydrogenation of compound* XLVc

Compound XLVc (492 mg) was hydrogenated in 25 ml glacial acetic acid with 170 mg prehydrogenated platinum oxide. Four moles of hydrogen were taken up in 9 hr. The catalyst was filtered off and the solution evaporated to dryness *in vacuo*. The residue was recrystallized from ether to give 369 mg material m.p. 204–209° which was used for the conversion into the compound XLVIIIb without further purification.

*Compound* XLVIIIb

The octahydro hexadeutero-α-oxoisopyrodelphinine (369 mg), prepared in the previous experiment, was heated with a solution of 16 g zinc chloride in 6 ml 5% hydrochloric acid to 40–60° for 90 min. The reaction mixture was diluted with water and continuously extracted with chloroform. The residue of the chloroform extract (332 mg) was crystallized from methanol–water until it reached a constant m.p. of 266°. This m.p. is the same as the m.p. of compound XLVIIIa which we have prepared according to Jacobs[15] in the same manner from unlabelled octahydo-α-oxoisopyrodelphinine. The two samples gave also no m.p. depression and had identical infrared spectra except for the presence of bands at 2065, 2210, 2240 $cm^{-1}$ in the spectrum of the labelled compound XLVIIIb. (Found: $OCH_3$, 10·71; 6·83 atom per cent XSS D. Calc. for $C_{29}H_{35}D_3O_7N$: $2OCH_3$, 11·97; 7·3 atom per cent XSS D.)

*Delphonine methiodide* XLIX

Delphonine (30 g) was heated under reflux with 200 ml n-butyl ether and 30 ml methyl iodide for 6 hr. The precipitate which has formed at the end of this period was filtered off and washed with ether. The yield was 36 g. This crude material was recrystallized several times from acetone until it reached the constant m.p. of 208–211°. (Found: C, 50·73; H, 7·02; I, 21·25; $OCH_3$, 20·44. Calc. for $C_{23}H_{42}O_7NI$: C, 50·42; H, 7·11; I, 21·33; $4OCH_3$, 20·77%.)

The methiodide was converted into the methohydroxide by filtering a methanolic solution through a column of amberlite IRA-400 in the hydroxyl form.

*Base degradation of delphonine methohydroxide to* LI

Delphonine methohydroxide (27·5 g) was divided into five equal portions and each of them was subjected to the following treatment. It was dissolved in 25 ml water and 10 ml saturated sodium hydroxide. This solution was heated on an oil bath (130–190°) until most of the water evaporated. This required a period of 2–4 hr, after which the mixture was diluted with water and extracted with

ether. The total yield of all five runs was 20·4 g of dark red-brown resin. This material was subjected to 3 countercurrent distributions in 9 funnels as follows:

(1) A distribution between 500 ml phosphate buffer pH 5·8 and 500 ml chloroform. Fractions 5, 6, 7 and 8 were combined and yielded 4 g of material which was subjected to the next distribution.

(2) A distribution between 500 ml phosphate buffer pH 5·45 and 500 ml chloroform. The combined fractions 3, 4, 5, 6 and 7 yielded 2·6 g of material which was subjected to the third distribution.

(3) A distribution between 400 ml phosphate buffer pH 5·45 and 400 ml chloroform. The fractions 5, 6 and 7 contained 370 mg of colorless oil which crystallized and was recrystallized from ether to a constant m.p. of 153°. (Found: C, 67·52, 67·52; H, 9·30, 9·02; $OCH_3$, 22·48. Calc. for $C_{28}H_{37}O_8N$: C, 67·78; H, 9·15; $3OCH_3$, 22·85%.) Infrared spectrum, ($HCCl_3$) no hydroxyl, 1706 $cm^{-1}$.

*The bis-2,4-dinitrophenylhydrazone of* LI

2,4-Dinitrophenylhydrazine (22·7 mg) was dissolved in a mixture of 0·5 ml ethanol, 5 drops conc sulphuric acid and 5 drops water. A solution of 25·5 mg of compound LI in 1 ml ethanol was then added and the mixture heated for 10 min on the steam bath. The entire reaction mixture was then washed with benzene on a column of 10 g basic alumina and eluted with 1% methanol in benzene. The substance was precipitated with chloroform from an ethanolic solution. It was microcrystalline m.p. 157°. (Found: C, 53·70; H, 5·73; N, 16·45; $OCH_3$, 12·37, 10·22. Calc. for $C_{33}H_{44}O_{11}N_8$: C, 54·74; H, 5·90; N, 16·41; $3OCH_3$, 12·12%).

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# ON THE STRUCTURE OF HUMULINONE

J. N. SHOOLERY, M. VERZELE* and F. ALDERWEIRELDT*
Varian Associates, Palo Alto, California

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**Abstract**—Two structures have been proposed for humulinone (II and III in Fig. 1). The high resolution NMR spectrum of this and related substances points to the five-membered ring structure II.

HUMULONE is the most important hops constituent. It has structure I. Humulinone is an oxidation product of humulone and was assigned structure II by two of us[1]; the oxidation being followed by an isomerization.

Howard and Slater[2] preferred a non-isomerized six-membered ring structure (III) for humulinone, and claimed to have proved this by preparing the tribenzoate of desoxytetrahydrohumulone† from tetrahydrohumulinone in 3 per cent yield. Although we could obtain the tribenzoate in 25 per cent yield starting from tetrahydrohumulone, all our attempts to obtain the tribenzoate from tetrahydrohumulinone failed. The oxidation of tetrahydrohumulone or of humulone to the corresponding tetrahydrohumulinone or humulinone respectively occurs in ether and saturated sodium bicarbonate solution. The sodium salt of the humulinone compounds being insoluble, these substances precipitate readily when formed.

We have found that humulone, when its concentration is high, can also precipitate as the solid sodium salt. A possible explanation of the result of Howard and Slater can be found in the contamination of their tetrahydrohumulinone by tetrahydrohumulone. The question of the humulinone structure (five or six-membered ring) was therefore still open.

High resolution NMR spectroscopy was used to study the problem. From this it became apparent that the hydroxyl hydrogens were of little use for the purpose. Rapid proton exchange results in excessive broadening of the bands, the positions of which were moreover dependent on concentration. Other portions of the spectra of humulone and humulinone were practically identical. Significant changes occurred only in those resonances that could be assigned to the $-CH_2$-groups of the sidechains. In order to be certain, about the assignments of given resonances to definite $CH_2$ groups, dihydrohumulone (IV) was studied. This derivative was obtained by partial reduction of humulone.[3] The spectra were recorded in various solvents and in varying concentrations. The best results were obtained in deuterated chloroform. A typical specimen of the relevant spectra is shown in Fig. 1.

A trace of tetramethylsilane was added as internal standard.[4] The distance from

* Ghent University, Belgium.

† The tetrahydroderivatives have saturated instead of unsaturated sidechains. The desoxy compound is a true phloroglucinol derivative, the tertiary OH-group of humulone being replaced by hydrogen.

[1] F. Alderweireldt and M. Verzele, *Bull. Soc. Chim. Belg.* **66**, 391 (1957).
[2] G. A. Howard and C. A. Slater, *J. Chem. Soc.* 1460 (1958).
[3] M. Verzele and M. Anteunis, *Bull. Soc. Chim. Belg.* **68**, 315 (1959).
[4] G. Van Dyke Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

the tetramethylsilane peak to the chloroform peak (still present in trace quantities) corresponds to 438 cps at 60 mc. The resolution obtainable for acetaldehyde on the NMR spectrometer at the moment of recording of the spectra of Fig. 1 was of the order of 0·4 cps for the width of the quadruplet bands measured at hal height. That the complex high molecular weight molecules do not give the same resolution under those conditions is a normal phenomenon.[5]

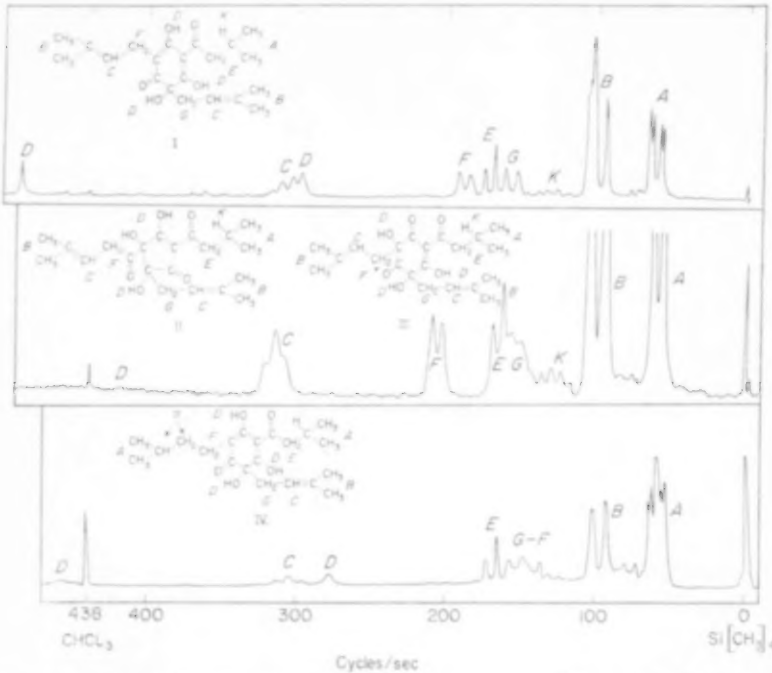


FIG. 1. Photographic reproduction on the same scale of the NMR spectra of humulone (upper), humulinone (middle) and dihydrohumulone (lower). The lettered resonances on the spectra derive from the identically labeled hydrogen atoms in the structural formulae.

As the protons are more depleted of their electrons, or as they are surrounded by more magnetically unshielding groups, their resonances fall at lower field values. This consideration together with a study of the relative surface area of the resonances corresponding with the number of hydrogen atoms that give rise to each particular band, permit assignment of the bands with reasonable certainty.

At about 60 cps from the tetramethylsilane peaks we find the resonances of the methyl groups labelled A; at about 100 cps the methyl groups labelled B; around 310 cps lies a triplet from the hydrogen atoms labelled C. Hydroxyl proton resonances are found at 294 and 480 cps in the humulone spectrum. An additional hydroxyl peak, found at very low field values (1150 cps) is not shown on the graph. The peak at 480 cps for humulone is not always sharp and is sometimes found as a low broad band stretching from 400 to 480 cps. The position of the peak at 294 cps in Fig. 1 is dependent on concentration. In the humulinone spectrum the broad band under the

[5] Varian Assoc., *Tech. Inf. Bull.* **2**, 1-n° 3 (1959).

chloroform peak is attributed to hydroxyl proton resonances. In the dihydrohumulone spectrum the OH peaks are found at 278 and 452 cps. The six resonances in humulone ranging from 152 to 190 cps must be ascribed to the $CH_2$ groups labelled E, F and G. Each group gives a doublet because of spin interaction with the one alpha hydrogen in each case. The central doublet at 166 and 173 cps has a characteristic shape which is found practically unchanged in humulinone (161–168 cps) and in dihydrohumulone (165–172 cps) and can therefore be attributed to the $CH_2$ group labelled E since it is the only one with unchanging environment in the three compounds. This is confirmed by studies in progress on other humulone derived substances. The humulone doublet at 183 and 190 cps has disappeared in dihydrohumulone and must belong to the $CH_2$ group labelled F. The remaining doublet at 152 and 159 cps is then caused by the $CH_2$ group G.

For a substance with structure III we would expect from the above considerations to obtain a NMR spectrum with a doublet of double intensity around 152–159 cps ($CH_2$ groups F and G in III), next to the unchanged doublet at about 166–173 cps. ($CH_2$ group E), but without a doublet at still lower field intensities. As seen in Fig. 1 this is not the case. A doublet about 50 cps lower than expected is found at values 203–208 in humulinone. This is in agreement with what we would expect for humulinone with structure II. The methylene group F attached to two double bonds in humulone has now become attached to one doubly bonded carbon and a carbonyl group. According to reference[5] the effective shielding constants of a doubly bonded carbon and a carbonyl group are 79 cps and 102 cps at 60 mc respectively (difference 23 cps). Counting on additivity of the shifts, which is very often the case[5] we would expect a downward resonance shift of about 23 cps going from the $CH_2$ group F in humulone to the same group in humulinone with structure II. This is in excellent agreement with the doublet found at 203–208 cps in humulinone (originally at 183–190 cps in humulone).

Taking into consideration the close reproducibility of the chemical shifts for all other $CH_2$ resonances in the three different compounds we think that the observed phenomena are significant and that NMR spectroscopy points quite definitely to a five-ring humulinone structure.

## EXPERIMENTAL

1. *Substances*

*Humulone* is obtained from hops extracts by precipitating the hop alpha acids as lead salts. Humulone is then separated from the other alpha acids (pre-, ad-, co- and posthumulone) by repeated crystallization of the *o*-phenylenediamine complex. The purity of the humulone was ascertained by partition chromatography, m.p. 70–71°.

*Humulinone* is obtained by oxidation (ether–sodium bicarbonate) of pure humulone[1], m.p. 72°.

*Dihydrohumulone*. Humulone was hydrogenated with 5% $PtO_2$ as catalyst in methanol brought to pH 5·0 with potassium-methylate. One mole of hydrogen is allowed to react. The product (2·5 g) was distributed (300 transfers) in a two-phase system of iso-octane as upper and a mixture with pH 7·6 of 15% triethanolamine; 0·6 N HCl; 25% ethyleneglycol as lower phase. Cells 140 to 170 afforded 510 mg dihydrohumulone. This was further purified by crystallization of the *o*-phenylenediamine complex until the m.p. of this reached 85°. The dihydrohumulone then obtained is a pale yellow oil and gives a single peak on re-distribution and in partition chromatographic purity assays.

2. *NMR Spectra*

All spectra were obtained from dilute solutions in deuterated chloroform. Each sample was diluted until broadening effects due to viscosity and intermolecular association were no longer observed.

The instrument used for the measurements was a Varian Associates Model V-4300 C High Resolution NMR spectrometer with a V-4012-SM 12" Electromagnet and VK-3506 Flux Stabilizer. Samples were placed in 5 mm thin-walled (0·37 mm) glass tubes and rotated at several hundred rpm by a small air turbine during the recording of the spectra. Calibration of peaks relative to the internal references $(CH_3)_4Si$ was accomplished by the standard audio-frequency sideband method, using a Hewlett–Packard 200-CD oscillator monitored continuously with a Hewlett–Packard 521 C Electronic Frequency counter.

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# TERPENOIDS—XXI*†

## THE STRUCTURE OF COSTUNOLIDE, A NEW SESQUITERPENE LACTONE FROM COSTUS ROOT OIL

A. SOMASEKAR RAO, G. R. KELKAR and S. C. BHATTACHARYYA
National Chemical Laboratory, Poona

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**Abstract**—Costunolide, the new sesquiterpene lactone isolated from costus root oil (*Saussurea lappa* Clarke) is shown to have the structure I on the basis of dehydrogenation, ozonolyses and the formation of santanolide 'C' under mild conditions.

THE costus plant, *Saussurea lappa* Clarke belongs to the compositae family. The essential oil obtained from costus roots is highly valued in perfumery as a blending agent.[1] The chemistry of costus oil has been studied by a number of workers particularly Semmler and Feldstein[2] and more recently by Romanuk *et al.*[3] Recently we have isolated costus oil from costus roots under mild conditions by a modified solvent extraction procedure with petroleum ether, details of which will be published shortly. The oil thus obtained is quite different from the oil examined by previous workers. One of the constituents of this oil is a new crystalline sesquiterpene lactone which we have named costunolide. This lactone is rather unstable particularly at elevated temperature. This may explain why the earlier investigators failed to detect its presence in costus root oil. This appears to be a primary constituent of costus oil. Two preliminary communications[4,5] dealing with its structure and absolute configuration have already been published.

Costunolide (I) is a lactone having the molecular formula $C_{15}H_{20}O_2$. It contains three double bonds as shown by catalytic hydrogenation. Complete hydrogenation gives the fragrant liquid hexahydrocostunolide (II) of the formula $C_{15}H_{26}O_2$. Hence costunolide (I) is monocarbocyclic. Partial hydrogenation of costunolide gives dihydrocostunolide (III). Costunolide (I), dihydrocostunolide (III) and hexahydrocostunolide (II) show I.R. bands at 1764, 1779 and 1764 $cm^{-1}$ respectively suggesting the presence of a $\gamma$-lactone.[6] While costunolide (I) gives 0·40 mole of formaldehyde on ozonolysis, dihydrocostunolide (III) gives only a trace on similar treatment. Costunolide (I) shows strong ultra-violet absorption ($\lambda_{max}$ 213 m$\mu$, log $\varepsilon$, 4·21) which is substantially reduced in dihydrocostunolide (III). Hence costunolide has a methylenic double bond (=$CH_2$) in conjugation with the carbonyl group of the lactone moiety. In agreement with this conclusion, costunolide consumes only two moles of

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[1] E. Guenther, *Essential Oils* **5**, 446 (1952).
[2] F. W. Semmler and Feldstein, *Ber. Dtsch. Chem. Ges.* **47**, 2433, 2687 (1914).
[3] M. Romanuk, V. Herout and F. Sorm, *Coll. Czech. Chem. Commun.* **23**, 2188 (1958).
[4] A. Somasekar Rao, G. R. Kelkar and S. C. Bhattacharyya, *Chem. & Ind.* 1359 (1958).
[5] S. C. Bhattacharyya, G. R. Kelkar and A. Somasekar Rao, *Chem. & Ind.* 1069 (1959).
[6] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, p. 153. Methuen, London (1954).

perbenzoic acid, the methylenic double bond being inert due to conjugation with the carbonyl group of lactone moiety.[7]

Lithium aluminium hydride reduction of costunolide (I) followed by selenium dehydrogenation of the crude diol (IV) gives 1,6-dimethyl naphthalene (V), presumably formed through initial cyclization of the diol (IV), followed by dehydrogenation with concomitant elimination of the $C_3$ unit, which in the parent compound necessarily

will be the seat of the lactonic moiety. Hydrogenation of dihydrocostunolide in acetic acid gives rise to a crystalline solid lactone (VI) m.p. 154–155° which is bicyclic as shown by its molecular formula and fully saturated nature. This on selenium dehydrogenation gives 1-methyl-7-ethyl naphthalene (VII). These observations suggest that though costunolide (I) is monocarbocyclic it can be readily converted to compounds based on the bicyclodecane system. Rigorous proof of the carbon skeleton of lactone (VI) follows from these data.

Costunolide (I), dihydrocostunolide (III) and the diol (VIII) obtained by lithium aluminium hydride reduction of dihydrocostunolide (III) give levulic acid on ozonolysis. In view of this and the nature of the carbon skeleton of lactone (VI), and the absence of conjugation in dihydrocostunolide (III), costunolide must be represented by structure I or Ia. Ozonolysis of dihydrocostunolide (III), esterification of the resulting acids with diazomethane and fractionation gave as the higher boiling

[7] Migrdichian, *Organic Synthesis* Vol. 2, p. 897. Reinhold, New York (1957).

portion, the compound IX having the molecular formula, $C_{11}H_{16}O_5$. On the basis of either formula I or Ia for costunolide, the compound IX must contain one ketogroup, one ester group and one $\gamma$-lactone group. In complete agreement with this expectation the I.R. spectrum of compound IX showed bands at 1718 (methyl ketone), 1756 (ester) and 1778 ($\gamma$-lactone) $cm^{-1}$. Compound IX forms a mono 2,4-dinitrophenylhydrazone, can be saponified to the acid XVIII of the formula $C_{10}H_{14}O_5$ and consumes 2 moles of hot alkali.

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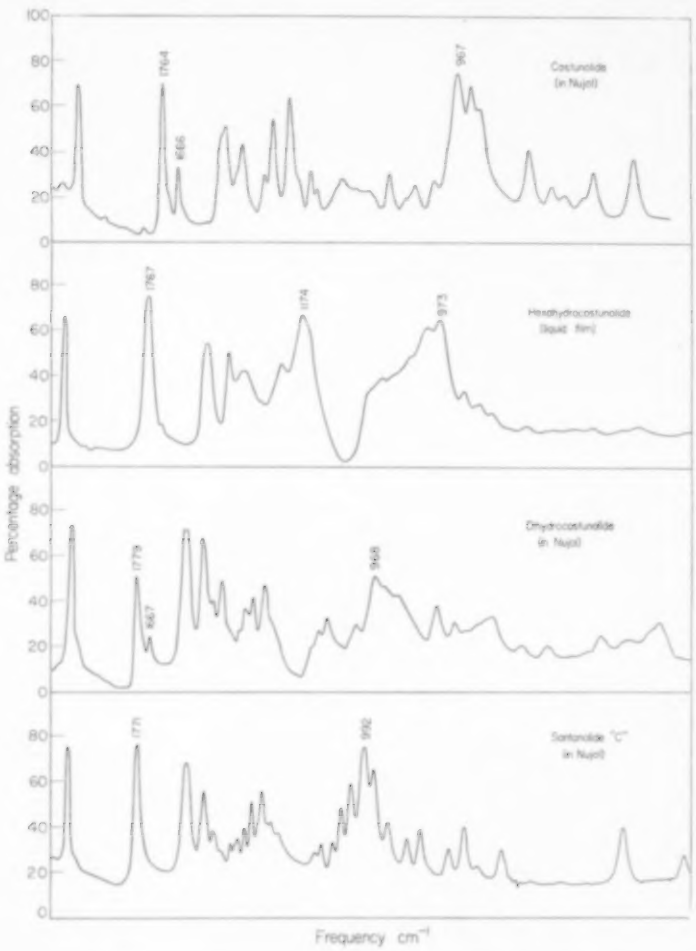



FIG. 1

Lithium aluminium hydride reduction of compound IX gives the tetrahydroxy compound X which reacts with sodium metaperiodate giving formaldehyde, thus showing the presence of two vicinal hydroxyl groups, in compound X. Costunolide undergoes hydrogenolysis during hydrogenation to give the acid XI. The diol VIII on oxidation with activated $MnO_2$ gives the $\alpha,\beta$-unsaturated ketone XII. These observations show that costunolide has the structure shown in I.

The facile cyclization of some of the members of costunolide series also supports the presence of a ten membered carbocyclic ring in costunolide. The crystalline lactone (VI) is a cyclized product as mentioned earlier. Dihydrocostunolide (III) can be cyclized to the cyclodihydrocostunolide (XIII). The bicyclic nature of XIII is shown by the molecular formula and the presence of only one double bond. The absolute configuration of the lactone (VI) at $C_6$ has been found by the molecular rotation difference method.[8] The molecular rotation difference ($\Delta M_{lactone\text{-}diol} = +144{\cdot}8$) between the saturated lactone (VI) and the corresponding diol (XIV) shows

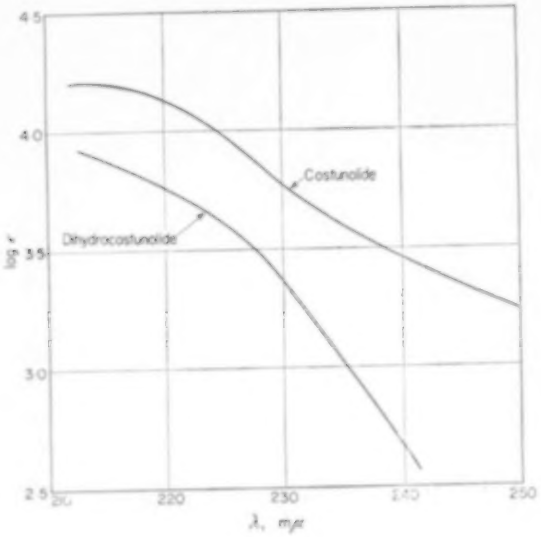



FIG. 2

that the lactone (VI) has the D-configuration at $C_6$. In the the region 700–1350 $cm^{-1}$ the lactone (VI) shows an intense band at 992 $cm^{-1}$ (Nujol) 994 $cm^{-1}$ (chloroform) which is far more intense than any other band in this region. Hence VI is a trans-lactone.[9] This leads to the assignment of $\beta$-configuration to the $C_7$ side-chain of lactone VI. The absolute configuration of costunolide (I) follows from the absolute configuration of the lactone (VI) at $C_6$ and $C_7$. At an early stage of our investigations, we suspected the identity of the lactone (VI) m.p. 154–155° with santanolide 'C' (m.p. quoted at that time 137–139°).[10] However, in view of the large difference in m.p. and rotation we were hesitant to come to a definite conclusion; but in a recent paper Herout and Sorm[11] have stated that the previous sample of santanolide 'C' m.p. 137–139° was impure; the pure sample of santanolide 'C' subsequently prepared by them has a m.p. 153–154° which is the same as that of compound VI. In view of this, and the similarity of infra-red spectra, the identity of lactone (VI) with santanolide 'C' may be taken as established.

The molecular rotation difference ($\Delta M_{lactone\text{-}diol} = -50$) between the hexa-hydrocostunolide (II) and the corresponding diol (XV) is negative whereas the

[8] V. Sykora and M. Romanuk, *Coll. Czech. Chem. Comm.* **22**, 1909 (1957).
[9] T. Kanzawa, H. Kamio, M. Sumi and M. Nishikawa, *J. Amer. Chem. Soc.* **80**, 3705 (1958).
[10] O. Kovacs, V. Herout, M. Horak and F. Sorm, *Coll. Czech. Chem. Comm.* **21**, 225 (1956).
[11] V. Herout and F. Sorm, *Chem. & Ind.* 1067 (1959).

molecular rotation difference ($\Delta M_{\text{lactone-diol}} = +52$) is positive in the case of corresponding compounds prepared from arctiopicrin,[12] though the absolute configurations of costunolide and arctiopicrin[12] are identical at $C_6$ and $C_7$. This suggests that probably the two $C_{15}H_{26}O_2$ lactones do not have identical absolute configurations at both $C_6$ and $C_7$. Considering the method of preparation employed by us, hexahydrocostunolide (II) must have the same configurations as costunolide at $C_6$ and $C_7$. In the case of the $C_{15}H_{26}O_2$ lactone ($[\alpha]_D = +26°$) prepared from arctiopicrin a change in configuration at $C_6$ is rather unlikely whereas a change at $C_7$ may be possible, during the preparation of ethylene thioketal from the keto-lactone (XIX). The conversion of coprostane-4-one to the ethylene thioketal of cholestane-4-one may be cited as an analogy.[13] Hence in all probability the $C_{15}H_{26}O_2$ lactone derived from arctiopicrin is a *cis*-lactone having the $C_7$ side chain α-oriented.

The importance of ten-membered ring (carbocylic) compounds in terpene biogenesis has been discussed in the literature.[14,15] Costunolide is the parent lactone of this group. Recently, Herout and Sorm[11] have come to similar conclusions about the structure and absolute configuration of costunolide isolated from *Artemisia balchanorum*.

## EXPERIMENTAL

All melting points and boiling points are uncorrected. Rotations were measured in chloroform. Ultra-violet spectra were taken in 95% alcohol. Microanalyses were carried out by Mr. Pansare and colleagues. Infra-red spectra were determined by Mrs. S. Das Gupta and Mr. Nagaraja Rao.

*Isolation of costunolide* (I)

Costus root oil obtained by modified solvent extraction method developed by us was diluted with four times its volume of petroleum ether (40–60°), cooled to 0°, seeded with costunolide and kept in the refrigerator for a week. The crystals (yield 15%) were filtered off and crystallized from methanol (3–4 ml. of methanol per gram of costunolide) avoiding excess heating. Needle shaped crystals were obtained. On heating they collapsed to a glassy mass at 106–107°. Rotation: $[\alpha]_D = +128°$ (*c*, 0·45).

U.V. spectrum: $\lambda_{max}$ 213 mμ (log ε, 4·21) I.R. spectrum (in Nujol): Bands at 2833 1764, 1666, 1443, 1376, 1323, 1287, 1244, 1202, 1174, 1133, 1054, 1019, 994, 967, 952, 942, 893, 874, 863, 850, 841, 815 and 782 $cm^{-1}$. (Found: C, 77·89, H, 8·78; mol.wt. by saponification 236·1. $C_{15}H_{20}O_2$ requires: C, 77·55, H, 8·68%; mol.wt. 232·3).

*Hexahydrocostunolide* (II)

A solution of costunolide (10·9 g) in alcohol (250 ml) was hydrogenated at room temp at 60 atm in the presence of platinum oxide (0·14 g) catalyst. The temperature was raised to 40° towards the end. After the hydrogenation was complete the catalyst was filtered off and the solvent evaporated. The residue was passed through alumina and distilled to give hexahydrocostunolide (II) as a fragrant liquid b.p. 135–138°/0·4 mm, $d_{30}^{30}$ 1·007, $n_D^{30}$ 1·4880, $[\alpha]_D = -25°$ (*c*, 3·6). (Found: C, 75·5; H, 11·0. $C_{15}H_{28}O_2$ requires: C, 75·58; H, 11·0%). On chromatography a fraction with $[\alpha]_D = -36°$ was obtained.

I.R. spectrum (liquid film): bands at 2833, 1764, 1451, 1374, 1334, 1287, 1230, 1174, 1043, 1006, 988, 973, 945, 929, 919, 888, 835, 803 and 764 $cm^{-1}$

Hexahydrocostunolide (II) can also be obtained by the hydrogenation of costunolide (I) in alcohol in the presence of platinum catalyst at atm press; but the hydrogenation is slow after the absorption of 1 mole of hydrogen.

[12] M. Suchy, M. Horak, V. Herout and F. Sorm, *Croatica Chem. Acta* **29**, 247 (1957); M. Suchy, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **24**, 1542 (1959).
[13] R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.* **78**, 1409 (1956).
[14] D. H. R. Barton and P. de Mayo, *J. Chem. Soc.* 151 (1957).
[15] M. Suchy, M. Horak, V. Herout and F. Sorm, *Chem. & Ind.* **894** (1957); I. Ognjanoff, D. Ivanoff, V. Herout, M. Horak, J. Pliva and F. Sorm, *Ibid.* 820 (1957).

*Dihydrocostunolide* (III)

Costunolide (I, 10 g) in alcohol was hydrogenated using 5% palladium–charcoal (0·5 g) as catalyst. The hydrogenation became extremely slow after the absorption of 1170 ml hydrogen. (temp 31°, press 710 mm), which corresponds to 1·03 moles hydrogen. The catalyst was filtered off and the alcohol removed under suction. The residue was taken up in ether, washed with sodium carbonate solution (to remove acidic products) and then with water. Removal of ether followed by crystallization of the residue from pet ether (40–60°) furnished 7·7 g dihydrocostunolide (III), m.p. 70–73°, which on recrystallization melted at 77–78°. Rotation: $[\alpha]_D = +113{\cdot}6°$ (*c*, 3·0). U.V. spectrum: no peak at 213 mμ. I.R. Spectrum (in Nujol): Bands at 2833, 1779, 1667, 1450, 1444, 1383, 1340, 1305, 1244, 1230, 1210, 1198, 1059, 1043, 994, 968, 952, 937, 884, 870, 850, 836, 811, 793, 758, and 719 $cm^{-1}$. (Found: C, 76·7; H, 9·48; $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

The sodium carbonate extract on acidification furnished 0·35 g of the acid XI. The mother liquor left after crystallization of dihydrocostunolide (III) m.p. 77–78°, was a liquid which had $[\alpha]_D = +76°$ (*c*, 1·7). Probably this contained the $C_{11}$ epimer of dihydrocostunolide (III). This was not further examined.

*Santanolide "C"* (VI)

Costunolide (I, 16·1 g) was hydrogenated in alcohol at atm press using platinum catalyst till the rate of hydrogenation became slow. The catalyst was filtered off and the solvent was removed under suction. The residue was dissolved in acetic acid and hydrogenated in the presence of platinum catalyst at room temp. Hydrogenation stopped after the absorption of nearly 2·8 moles hydrogen (1·2 moles in alcohol, 1·6 moles in acetic acid medium). The catalyst was filtered off and solvent removed at 100° using a water pump. The residue was taken in ether and washed with sodium carbonate solution and then with water. Removal of ether furnished 13 g residue.

This residue (20 g, from two batches) was dissolved in ether and cooled to −5°. The solid which separated was filtered off and recrystallized twice from petroleum ether (40–60°) to furnish santanolide 'C' (VI) as glistening plates m.p. 154–155° (yield 2·4 g). Rotation: $[\alpha]_D = +55{\cdot}1°$ (*c*, 3·5) lit[10,11] m.p. 137–139°; 153–154°. $[\alpha]_D = +92{\cdot}2°$.[10]

The lactone (VI) does not show strong absorption in the U.V. region, it does not react with perbenzoic acid; in the I.R., there is no band in the region around 1650 $cm^{-1}$; all these data go to show the absence of a double bond in lactone (VI). The lactone (VI) gradually dissolves in hot alkali and can be recovered unchanged from the alkaline solution on acidification.

I.R. spectrum (Nujol): bands at 2865, 1771, 1464, 1452, 1380, 1345, 1282, 1262, 1241, 1220, 1193, 1169, 1075, 1062, 1041, 1030, 1014, 992, 977, 958, 935, 918, 887, 870, 858, 835, 748 and 713 $cm^{-1}$. For comparison with santanolide 'C'[10] the I.R. spectrum was also determined in chloroform solution and found to be almost identical with that of santanolide 'C'.[10] (Found: C, 76·33; H, 10·10; $C_{15}H_{24}O_2$ requires: C, 76·22, H, 10·24%).

The mother liquor left after the crystallization of lactone VI on chromatography gave the hexahydrocostunolide (II) as a liquid b.p. 160°/1·5 mm (bath, $[\alpha]_D = -25°$ (*c*, 3·5). I.R. spectrum was identical with that of hexahydrocostunolide (II) obtained by previous method.

*Isolation of the acid* (XI)

Costunolide (10 g) was hydrogenated in alcohol using 5% palladium charcoal as catalyst. The hydrogenation was stopped after the absorption of 1·2 moles hydrogen. The catalyst was filtered off and the solvent removed. The residue was taken in ether and shaken with sodium bicarbonate solution. The sodium bicarbonate extract on acidification followed by extraction with ether and removal of solvent furnished 1·5 g of the crude acid (XI). This was esterified with diazomethane in the usual way to give the methyl ester (XVI) b.p. 130°/0·6 mm. (bath) (Found: C, 76·5; H, 9·9. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47%).

The methyl ester (XVI) on lithium aluminium hydride reduction in the usual way (see below for a representative example) furnished the alcohol (XVII) as a liquid b.p. 135–140°/0·05 mm (bath). (Found: C, 80·6; H, 11·9; $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

*Diol* (IV)

Costunolide (7·0 g) dissolved in ether (150 ml) was added slowly to a suspension of lithium aluminium hydride (1·2 g) in 100 ml ether at 0°. After stirring at 0° for 1 hr, and heating to reflux

for 1½ hr, the reaction mixture was cooled, and the excess of lithium aluminium hydride decomposed carefully by adding dropwise cold water. The aluminium hydroxide was filtered off and washed thoroughly with ether. The ether layer was washed with water. Removal of solvent gave the diol IV (7·0 g) as a glassy material. A small portion was distilled to give slightly impure diol (IV) b.p. 160–180°/$10^{-3}$ mm (bath). (Found: C, 74·98; H, 10·07; $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

*Selenium dehydrogenation of the diol* (IV)

The crude diol (IV, 6·6 g) was mixed with selenium (7·1 g) and heated in nitrogen atmosphere at 300° for 48 hr. Distillation furnished 1·00 g distillate (V) b.p. 128–135°/9 mm which was purified by distillation over sodium. The clear distillate thus obtained was characterized as 1,6-dimethylnaphthalene through (i) picrate (crystallized from alcohol), m.p. and mixed m.p. with an authentic sample 111°, lit.[16] m.p. 110–111°. (Found: C, 55·63; H, 3·67; N, 11·3. $C_{18}H_{15}N_3O_7$ requires: C, 56·1; H, 3·92, N, 10·91%), (ii) s-trinitrobenzene complex (crystallized from alcohol), m.p. and mixed m.p. with an authentic sample 130–131°, lit[16] m.p. 131–132°. (Found: C, 59·38; H, 3·63, N, 11·8. $C_{15}H_{15}N_3O_6$ requires: C, 58·53; H, 4·09; N, 11·38%).

*Selenium dehydrogenation of the lactone* (VI)

The lactone (VI, 1·2 g) was heated with selenium (1·6 g) at 270–300° for 48 hr in nitrogen atmosphere. The product was distilled off at 2 mm (bath temp 200° towards the end). To remove the lactonic impurities the distillate was heated on a steam bath for 1½ hr with an aqueous alcoholic solution of potassium hydroxide (1.2 g potassium hydroxide, 10 ml water and 2 ml alcohol). It was then diluted with water and extracted with ether. The ether extract on solvent removal, followed by chromatography of the residue (0·20 g) on $Al_2O_3$ (grade I, 10 g) furnished a clear liquid (0·16 g) which gave a s-trinitrobenzene complex (from alcohol) m.p. 99–102°. After two recrystallizations the m.p. rose to 107–108° alone or when mixed with an authentic sample of s-trinitrobenzene complex of 1-methyl-7-ethylnaphthalene prepared from hexahydrosantonin. (Found: C, 60·02; H, 4·79; N, 11·4 (for the sample from lactone (VI); C, 60·32; H, 4·38; N, 11·2 (for the sample from hexahydrosantonin); $C_{19}H_{17}N_3O_6$ requires; C, 59·53; H, 4·47; N, 10·96%).

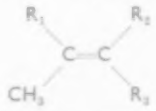
*Ozonolysis*

(i) *Estimation of formaldehyde*

Costunolide (I, 0·26 g) was dissolved in chloroform (75ml) cooled to 0° and a stream of ozonized oxygen (0·3 g of ozone per hr) was passed for 3 hr. The ozonized solution was steam distilled treated with dimedone solution and the chloroform removed by distillation. The formaldimethone m.p. 180–186° which separated weighed 0·132 g (0·40 moles). After one crystallization the sample of formaldimethone melted alone or on admixture with an authentic sample at 190–191°.

Dihydrocostunolide (III, 0·30 g) under similar conditions gave only 12 mg precipitate m.p. 176–184°.

(ii) *Ozonolysis of costunolide* (I) *and the estimation of the group*




Costunolide (I, 9·4 g) was dissolved in ethyl acetate, cooled to 0° and a stream of ozonized oxygen was passed till the ozonolysis was complete. The solvent was removed at 50° (towards the end the pressure was 2 mm). The residue was carefully heated with water on a water bath, for 2 hr. A clear solution was obtained. This was made up to 150 ml; 0·5 ml of the aqueous solution was taken and the number of —CO·$CH_3$ groups estimated by the consumption of iodine in alkaline medium[17] (Found: number of methyl ketone groups = 2·3 calculated for the structure (I) = 2·0). The higher value found experimentally may be due to the presence of aldehydes.

[16] C. F. Seidel, P. H. Muller and H. Schinz, *Helv. Chem. Acta* **27**, 738 (1944).
[17] Scott, *Standard methods of Chemical Analysis Vol.* 2, p. 2136. Van Nostrand, New York (1939).

The remaining part of the aqueous solution was separated in the usual way to the following fractions: (A), neutral, volatile; (B) neutral, non-volatile; (C) volatile acids; (D) non-volatile acids. Fractions A and B were not studied. The presence of formic acid in fraction C was shown by chromotropic acid test.[18] Fraction D was esterified with diazomethane and fractionated to give three fractions: (i) b.p. 88–91°/15 mm (1·68 g); (ii) b.p. 60–80°/3 mm (0·75 g); (iii) b.p. 125–150°/3·5 mm (0·62 g). Fraction (i) $n_D^{25} = 1{\cdot}4164$ (Found: C, 54·84; H, 7·67; $C_6H_{10}O_3$ requires: C, 55·4; H, 7·7%) gave a 2,4 dinitro phenylhydrazone m.p. and mixed m.p. with an authentic sample of methyl levulinate 2,4-dinitro-phenylhydrazone 140–141° (Found: C, 46·30; H, 4·31, $C_{12}H_{14}N_4O_6$ requires: C, 46·45; H, 4·55%). Hence fraction (i) is identified as methyl levulinate.[19]

Fractions (ii) and (iii) were not studied critically.

*Diol* (VIII). Dihydrocostunolide (III, 9·0 g) was reduced with lithium aluminium hydride (3·0 g) in ether (200 ml) in the usual way. After the reaction was complete the mixture was cooled and the excess of lithium aluminium hydride decomposed with ice water. The aluminium hydroxide was filtered off and washed with ether. The ether layer on solvent removal gave the diol (VIII) $[\alpha]_D = +35{\cdot}1°$ as a syrup. This was used as such for the next step. I.R. spectrum (liquid film) no band at 1779 $cm^{-1}$ (absence of γ-lactone), strong band at 3315 $cm^{-1}$ (hydroxyl group).

(iii) *Ozonolysis of the diol* (VIII)

The diol (VIII, 6·2 g) was ozonized and worked up in the same way as mentioned earlier. Methyl levulinate (yield 1·3 g) was identified through its 2,4-dinitrophenylhydrazone m.p. and mixed m.p. with an authentic sample 140–141° (Found: N, 18·3%; $C_{12}H_{14}N_4O_6$ requires: N, 18·06%). The other fractions were not studied critically.

(iv) *Ozonolysis of dihydrocostunolide* (III)

Dihydrocostunolide (III, 17·6 g) was ozonized in ethyl acetate solution. It was worked up in the usual way. The acidic portion weighed 19·6 g. This was esterified with diazomethane and fractionated when two fractions were obtained. Fraction (i) b.p. 70–84/4·5 mm (mostly at 70–72°), (Yield 5·9 g) has been identified as methyl levulinate. Fraction (ii) b.p. 130–160°/0·4 mm (wt 10·3 g) was refractionated and the portion (IX) b.p. 180–185°/3 mm was analyzed. $n_D^{28}$ 1·4620. Rotation: $[\alpha]_D^{25} = 0°$ (*c*, 5·0). (Found: C, 57·7; H, 7·2. Eq. wt. by saponification 113. $C_{11}H_{16}O_5$ requires: C, 57·88; H, 7·07%. Eq. wt. 114).

Compound IX gave a yellow 2,4-dinitrophenylhydrazone m.p. 94–95° (Found: N, 13·6. $C_{17}H_{20}O_8N_4$ requires: N, 13·72%).

*Saponification of ester* (IX). The ester (IX, 1·4 g) was heated for 2 hr on a water bath with an alcoholic solution of potassium hydroxide (1·3 g potassium hydroxide, 2·5 ml water, 10 ml alcohol). The saponified solution was diluted and extracted with chloroform to remove unsaponified ester (IX). The aqueous layer was made acidic and heated on a water bath for 1 hr. It was then extracted with chloroform in a liquid–liquid extractor. The chloroform extract on solvent removal followed by distillation of the residue furnished the acid (XVIII), b.p. 150–170°/0·002 mm (bath, 1·2 g) (Found: C, 55·6; H, 6·6. $C_{10}H_{14}O_5$ requires: C, 56·07; H, 6·59%).

*Lithium aluminium hydride reduction of ester* (IX).

The ester (IX, 0·5 g) was reduced by lithium aluminium hydride (0·5 g) suspended in ether (30 ml, 1½ hr at 0°; 5 hr at 45°). After the reduction was complete the excess lithium aluminium hydride was decomposed carefully with cold water. Enough dilute sulphuric acid (2 N) was added to dissolve the precipitate. The aqueous solution was extracted twice with ether and the ether extracts rejected. The aqueous layer which contained the tetrahydroxy compound (X) was neutralized with sodium carbonate solution and the precipitate obtained was filtered off. The filtrate was concentrated to a small volume and extracted with chloroform for 24 hr in a liquid–liquid extractor. The chloroform extract on solvent removal gave 0·4 g residue which was dissolved in water, filtered and the filtrate concentrated in vacuum. The tetrahydroxy compound (X) thus obtained did not crystallize. On treatment with

[18] Feigl, *Spot tests in Organic Analysis* p. 340. Elsevier, New York (1956).
[19] Heilbron and Bunbury *Dictionary of Organic Compounds* Vol. 3, p. 178. Eyre and Spottiswoode, London (1953).

sodium metaperiodate solution the crude tetrahydroxy compound (X) gave formaldehyde (estimated as formaldimethone) in nearly quantitative yield.

*Lithium aluminium hydride reduction of the lactone* (VI). The lactone (VI) was reduced by lithium aluminium hydride in the usual way. The diol (XIV) was obtained as needle shaped crystals m.p. 116–117° (crystallized from benzene–petroleum ether mixture). Rotation: $[\alpha]_D^{27} = -6{\cdot}2$ (*c*, 4·8). (Found: C, 74·95; H, 11·5. $C_{15}H_{28}O_2$ requires: C, 74·95; H, 11·74%).

I.R. spectrum (Nujol): Bands at 3110, 2820, 1452, 1374, 1341, 1261, 1053, 1040, 1019, 1002, 974, 961, 945, 917 892, 869 ,853 and 832 $cm^{-1}$.

*Diol* (XV). Hexahydrocostunolide (II, 2·2 g) ($[\alpha]_D = -32°$) (purified by chromatography) was reduced with lithium aluminium hydride (0·5 g) in the usual way to give the diol (XV), b.p. 153–155°/ 0·4 mm (evaporative distillation). $[\alpha]_D = -11°$ (*c*, 2·1). (Found: C, 74·03; H, 11·95. $C_{15}H_{30}O_2$ requires: C, 74·32; H, 12·48%). I.R. spectrum: No band at 1764 $cm^{-1}$ (absence of $\gamma$-lactone). Strong band at 3310 $cm^{-1}$ (hydroxyl group).

*Cyclodihydrocostunolide* (XIII). Dihydrocostunolide (III, 0·15 g) was heated to reflux with acetic acid (1 ml) and acetic anhydride (1 ml) for 4 hr. The solvent was removed under suction. The residue was taken up in ether and washed with sodium carbonate solution. The ether extract on solvent removal followed by short-path distillation in vacuum (1 mm) gave 0·13 g cyclodihydrocostunolide (XIII) which had the m.p. 120–122° after two crystallizations from pet ether (Found: C, 77·4; H, 9·4. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%). The compound (XIII) after 8 crystallizations showed a m.p. 134–136° lit[20,11] m.p. 136–7°; 135·5.

*The* $\alpha,\beta$*-unsaturated ketone* (XII). The diol (VIII, 0·15 g) was dissolved in pet ether (40–60°) and shaken with activated $MnO_2$ at room temp for 24 hr. The manganese dioxide was filtered off. The filtrate on removal of solvent at 40° gave a viscous oil which appears to be impure $\alpha,\beta$-unsaturated ketone (XII). U.V. spectrum: $\lambda_{max}$ 229 m$\mu$; log $\varepsilon$ 3·2. No attempt was made to isolate the pure $\alpha,\beta$-unsaturated ketone (XII).

[20] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956).



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Tetrahedron 1960, Vol. 9, pp. 284 to 288. Pergamon Press Ltd. Printed in Northern Ireland

# THE STRUCTURE AND CHEMISTRY OF HYDROXYLYCOCTONINE

Z. VALENTA and I. G. WRIGHT
Chemistry Department, University of New Brunswick, Fredericton, N.B.

(*Received* 24 *December* 1959)

**Abstract**—The observed physical properties and some selected reactions define hydroxylycoctonine as IV and its anhydronium salts as III.

THE remarkable X-ray analysis of a derivative of lycoctonine led to structure I for this complex di-terpene alkaloid.[1,2] A majority of the results of the extensive degradation studies of Edwards *et al.*[3] were easily explicable by this structure, which was also recognized as being eminently sound biogenetically.[4,5] The skeleton of structure I clearly differs from a noratisine skeleton only by the additional $C_7$—$C_{17}$ bond and by the presence of a $C_9$—$C_{10}$ bond in place of a $C_8$—$C_{10}$ bond. The elucidation of the structure of delphinine[6] and aconitine[7] (confirmed by an X-ray analysis[8]) established that the carbon skeleton of I is generally present in polyoxygenated di-terpene alkaloids.

However, some experimental results in lycotonine chemistry were not easily explicable on the basis of structure I for lycoctonine. It was found, for example, that lycoctonine, $C_{25}H_{41}O_7N$, is easily oxidized with silver oxide[9] or lead tetra-acetate[10] to hydroxylycoctonine, $C_{25}H_{41}O_8N$. A drastic change in basicity (lycoctonine: $pK_a$ = 8·8; hydroxylycoctonine: $pK_a$ = 5·6 in 50 per cent methanol) indicated that the reaction very likely took place in the environment of the nitrogen atom. Hydroxylycoctonine could be oxidized with potassium permanganate to the lactam hydroxylycoctonam, $C_{25}H_{39}O_9N$, which on vigorous acid treatment yielded ethylamine.[9] These transformations indicated that the additional oxygen function in hydroxylycoctonine is attached to $C_{17}$. Cookson and Trevett reported that hydroxylycoctonine forms crystalline anhydronium salts (perchlorate, $C_{25}H_{40}O_{10}NCl$ and iodide, $C_{25}H_{40}O_6NI$) which show strong maxima in the infra-red spectrum at 1710 $cm^{-1}$ and 1660 $cm^{-1}$ and can be reconverted into the parent base on treatment with alkali.[10] This result can clearly not be reconciled with the structure II which was considered for hydroxylycoctonine by Edwards *et al.*[3]

In a preliminary communication, we proposed that hydroxylycoctonine must be

[1] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[2] Formula I implies absolute stereochemistry which was established crystallographically. M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1843 (1959).
[3] O. E. Edwards, L. Marion and D. K. R. Stewart, *Canad. J. Chem.* **34**, 1315 (1956).
[4] Z. Valenta and K. Wiesner, *Chem. & Ind.* 354 (1956).
[5] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 3121 (1956).
[6] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron Letters* No. 3, 11 (1959).
[7] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters* No. 2, 15 (1959).
[8] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1116 (1959).
[9] O. E. Edwards and L. Marion, *Canad. J. Chem.* **30**, 627 (1952); **32**, 1146 (1954).
[10] R. C. Cookson and M. E. Trevett, *Chem. & Ind.* 276 (1956).

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IV formed by the hydration of III.[11,12] The remarkable formation of III in the oxidation of lycoctonine with lead tetra-acetate or silver oxide can be visualized either as a concerted reaction (as indicated by arrows in formula I) or as a cyclic reaction of the type commonly assumed for lead tetra-acetate and periodate oxidations.[13] Structure IV for hydroxylycoctonine cannot be considered as rigorously proven chemically, but follows logically from its physical and chemical properties. The unusual stability of the intramolecular hydrate has precedents in other cyclic compounds. It was found, for instance, that an oxidation product of delphonine (partial formula VIII) was almost completely hydrated since it showed no peaks in the infra-red carbonyl region.[14,15]

The significantly lower basicity of hydroxylycoctonine must have its explanation in the fact that the hydrated form (IV) is the important species in the base-conjugate acid equilibrium. The low p$K_a$ value is readily reconcilable with the carbinolamine ether grouping present in IV. The spectroscopic results also find a ready explanation in this formulation.

One interesting experimental result of Edwards *et al.*[3] deserves comment at this point. They reported that lycoctonamic acid methyl ester (partial formula Ia) hydrolysed rapidly with base, while the corresponding ester in the hydroxylycoctonine series IVa was almost completely inert under the same conditions. Since the additional C—O grouping of hydroxylycoctonine cannot be in a direct proximity to the carbomethoxyl group, the effect must clearly be a conformational one. As can be seen from the two formulae, the formation of the oxygen ring in IVa displaces the $C_6$-methoxyl group in the direction of the $C_4$-carbomethoxyl group, and increases the steric hindrance at the reaction site.

Since we were in the possession of a relatively large amount of lycoctonine, obtained from the roots of *Inula royleana* DC,[16,17] we decided to study hydroxylycoctonine by additional experiments. Hydroxylycoctonine was reduced with sodium borohydride in methanol to a crystalline compound, $C_{25}H_{43}O_7N$, m.p. 173–175°,

[11] Z. Valenta, *Chem. & Ind.* 633 (1959).

[12] Professor G. Büchi, Massachusetts Institute of Technology, explained independently the formation and properties of hydroxylycoctonine by structures III and IV.

[13] A partial formula of lycoctonine in which the pertinent part of the molecule is drawn in the Newman convention (looking along the $C_7$–$C_{17}$ axis) shows that a cyclic reaction should certainly be possible. It

appears quite likely that the oxidation with silver oxide is facilitated by the formation of a favourable cyclic complex, since this mild oxidizing agent does not usually split 1,2-aminoalcohols.

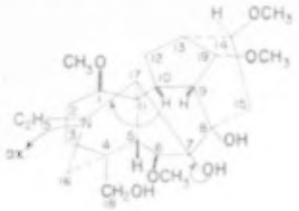
[14] Professor K. Wiesner, personal communication.

[15] The observation of Lyle *et al.* that the salts of 1-methyl-4-piperidone and 1-methyl-3-piperidone crystallize with one molecule of water and do not absorb in the carbonyl region of the infra-red spectrum is significant in this connection. [R. E. Lyle, R. E. Adel and G. G. Lyle, *J. Org. Chem.* **24**, 342 (1959).] The formation of an intramolecular hydrate between the two unsaturated functions of (III) is then simply a consequence of a favourable steric arrangement.

[16] A. Khaleque, S. Papadopoulos, I. G. Wright and Z. Valenta, *Chem. & Ind.* 513 (1959).

[17] O. E. Edwards and M. N. Rodger, *Canad. J. Chem.* **37**, 1187 (1959).

which had no carbonyl peaks in the infra-red spectrum. In consideration of the properties of hydroxylycoctonine this change is best explained as an elimination of water and the reduction of a ketone and a $\overset{(+)}{C}=N$ grouping to the triol (V). The correctness of structure V could be established by an oxidation with periodic acid which gave in a fast reaction and an excellent yield the hemiacetal ketone (VI), $C_{25}H_{41}O_7N$. The absence of a five-membered ring ketone peak in the infra-red spectrum of VI together with the fact that the correctly analyzing oily monoacetate VII (prepared from VI in two steps) did not contain a hydroxyl group establishes the functionality of this compound.



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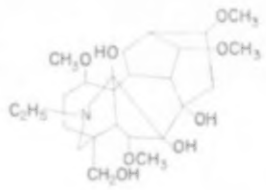

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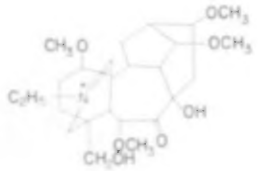
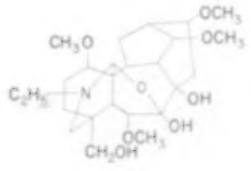


III



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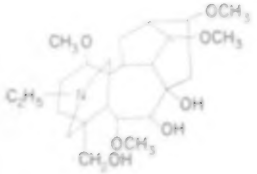

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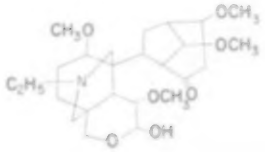

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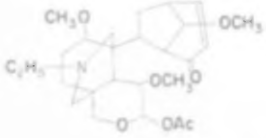
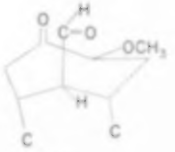
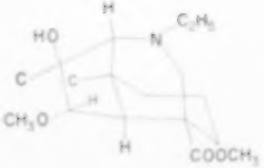


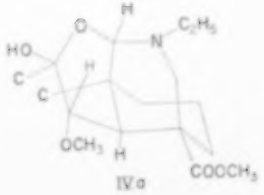
VII



VIII



Ia



IVa

Treatment of VI with silver oxide in methanol yielded a water soluble material which, according to its infra-red spectrum, was clearly an amino acid. It was not further investigated.

At the present time we have no rigorous proof for the configuration of the secondary alcohol group in V. However, it was observed in a preliminary experiment that the diacetate of V slowly loses a molecule of acetic acid on sublimation. Therefore, the hydroxyl group is very likely *trans* to the $C_6$-methoxyl group. There is no doubt that this methoxyl group has the same configuration in V and III as in I. While equilibration of this group is possible in III due to the α-keto group, a conformational analysis clearly shows the greater stability of the original lycoctonine configuration at $C_6$.

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While this work was in progress Edwards *et al.* reported additional experiments in the hydroxylycoctonine series[18] which led them to propose independently the structure III for the anhydronium salts. In this new communication, they retained structure II as the representation of hydroxylycoctonine.[19] The two series of experiments establish the correctness of structure III as the expression for the anhydronium salts.

Thus it can be seen that the formation and the properties of hydroxylycoctonine not only can be rationalized on the basis of formula I for lycoctonine, but provide an important chemical information about the relationship of the nitrogen ring and the B-ring in lycoctonine.

## EXPERIMENTAL

*Triol* V. Sodium borohydride (6 g) was added cautiously to a cooled solution of hydroxylycoctonine (2·66 g) in methanol (50 ml). The solution was heated under reflux for 2·5 hr, concentrated, diluted with 100 ml water and extracted with chloroform. The dried extract was purified by a countercurrent distribution in nine funnels between chloroform and a citric acid–phosphate buffer (pH 3·6) with chloroform as the moving phase. The material in the first four funnels (1·33 g) was recrystallized repeatedly from aqueous acetone and gave V, m.p. 173–175° (Found: C, 63·71; H, 9·09; O, 23·73; N, 2·91; act. H, 0·631. $C_{23}H_{43}O_7N$ requires: C, 63·94; H, 9·23; O, 23·85; N, 2·98; three act. H, 0·642%. Fractions 6–9 of the distribution contained an oily material which was not further investigated.

*Hemiacetal* VI. Triol V (252 mg) was treated with a 1% periodic acid solution (50 ml) for 30 min at room temp. The excess of the oxidizing agent was destroyed by adding ethylene glycol (2 ml) and the reaction mixture was evacuated for a few minutes to remove formaldehyde. Basification of the solution with sodium bicarbonate and extraction with chloroform yielded 240 mg of an oily material. Chromatography of this product on acid washed alumina (8 g) and study of the individual fractions by infra-red spectroscopy showed it to be homogeneous. A top chromatographic fraction was dried for analysis as a foam at 70° for 48 hr. (Found: C, 63·91; H, 8·60; O, 24·46; $OCH_3$, 25·03. $C_{23}H_{41}O_7N$ requires: C, 64·21; H, 8·84; O, 23·95; four $OCH_3$, 26·55%). I.R. (chloroform) 1707 $cm^{-1}$. The compound could not be sublimed, since heating to 200° resulted in partial elimination of methanol.

*Acetate* VII. Hemiacetal VI (100 mg) was treated overnight at room temp with a mixture of conc HCl (10 ml) and ethanol (10 ml). The solution was partially evaporated, treated with 5% aqueous $H_2SO_4$, washed with chloroform and basified with sodium carbonate. Extraction of the basic aqueous layer with chloroform yielded oily material (96 mg), ν I.R. (chloroform) 1675 $cm^{-1}$. The impure unsaturated ketone was reacted for 12 hr at room temp with a mixture of acetic anhydride (12 ml) and pyridine (12 ml). The solution was evaporated under reduced pressure and the residue was distributed between chloroform and 5% aqueous $H_2SO_4$. Basification of the aqueous layer with sodium carbonate, extraction with chloroform and evaporation of the solvent yielded an oily product (92 mg) which was chromatographed on acid washed alumina (3 g). Elution with 1% methanol in

[18] O. E. Edwards, M. Los and L. Marion, *Proc. Chem. Soc.* 192 (1959).

[19] Experimental details together with the acceptance of structure IV for hydroxylycoctonine were published by the National Research Council authors after the completion of this manuscript. [O. E. Edwards, M. Los and L. Marion, *Canad. J. Chem.* **37**, 1996 (1959).]

chloroform gave the desired oily acetate VI (43 mg), νI.R. (chloroform) 1735, 1675 $cm^{-1}$, no OH peak; $\lambda_{max}$ 226 mμ, which was sublimed for analysis at 180°/0·02 mm. (Found: C, 65·01; H, 7·92; O, 23·73; $OCH_3$, 19·21; C—$CH_3$, 4·31; acetyl, 7·85. $C_{24}H_{38}O_7N$ requires: C, 65·38; H, 8·23; O, 23·73; 3($OCH_3$), 19·50; 2(C—$CH_3$), 6·28; acetyl, 8·80%).

*Oxidation of* VI *with silver oxide.* Hemiacetal VI (22 mg) was shaken for 24 hr with freshly prepared silver oxide in 80% aqueous methanol. Filtration and concentration under reduced pressure, dilution with water and extraction with chloroform yielded an oil (9 mg) which according to its infra-red spectrum was a mixture of VI and the corresponding α,β-unsaturated ketone. Evaporation of the aqueous solution to dryness gave an oily residue (13 mg), νI.R. (chloroform) 3400–3000, 1710, 1603 $cm^{-1}$ (carboxylate).

Tetrahedron, 1960, Vol. 9, pp. 289 to 294. Pergamon Press Ltd. Printed in Northern Ireland

# SYNTHESES OF AMINO ALKYL SULPHONIC ACIDS AND THEIR PEPTIDE ANALOGUES[1]

M. FRANKEL and P. MOSES
Department of Organic Chemistry, The Hebrew University, Jersualem

(*Received* 17 *November* 1959)

**Abstract**—New amino alkyl sulphonic acids have been synthesized, including some substituted derivatives and several peptide analogues containing the —CO·NH— group formed from amino acid and amino alkyl sulphonic acid components. Peptide-like compounds containing the —$SO_2$·NH— group were prepared from N-substituted taurine and esters of amino acids. Theoretical aspects underlying the reactions involved are discussed.

THE amino sulphonic acids, structurally related to amino acids, are of interest from the chemical and also the biological standpoint, e.g., as potential anti-metabolites.

Baker and Mulder[2] prepared a number of α-amino sulphonic acids and McIlwain[3] extended the study of these compounds and tested some for their inhibitory effect on the growth of micro-organisms.[4]

The aim of this investigation was the synthesis of new amino alkyl sulphonic acids and of peptide-like compounds derived from them. These compounds were tested for their inhibitory effect on the growth of micro-organisms; in addition, their effect on the growth of tumours are under investigation.

New amino alkyl sulphonic acids were obtained by modifications of the methods of McIlwain.[3] Unlike the α-amino acids, the α-amino alkyl sulphonic acids are unstable in acid and alkali solutions, decomposing to aldehyde, sulphur dioxide and ammonia. It is suggested that in these compounds the lability of the sulphonic acid group is further increased by the presence of the amino group; the free electron pair on the nitrogen atom is capable of undergoing electromeric shift to form the unstable imine,[5] with rupture of the carbon-sulphur bond and loss of proton.

Acylation or benzoylation of the amino group greatly enhances the stability of these compounds; the electron pair of the nitrogen is able to participate in an electromeric shift with the carbonyl group, thus suppressing the tendency of the compound to revert to the unstable imine.[5]

The coupling of the α-amino alkyl sulphonic acids with a second amino acid

[1] Abstracted from a thesis submitted by P. Moses to the Senate of the Hebrew University in partial fulfilment of the requirements for the Ph.D. (1959).
[2] H. J. Backer and H. Mulder, *Rec. Trav. Chim.* **52**, 454 (1933); *Ibid.* **53**, 1120 (1934).
[3] H. McIlwain, *J. Chem. Soc.* 75 (1941).
[4] H. McIlwain, *Brit. J. Expt. Path.* **22**, 148 (1941).
[5] L. E. Hinkel, E. E. Ayling and J. H. Beynon, *J. Chem. Soc.* 184 (1936).

component, to form compounds analogous to peptides but containing the sulphonamide group was unsuccessful by adaptations of the known methods of peptide synthesis.[6–9] The failure of the α-amino alkyl sulphonic acids to couple with an amino acid is probably due to the instability of the former as well as to the relative lack of readiness on the part of the sulphur atom to act as an electron-acceptor towards the

amino group of the second amino acid component. This relative inactivity of the sulphur atom may be attributed to the limited polarisability of the sulphonic acid group as compared to that of the carbonyl group of the amino carboxylic acids.[10] The reluctance of the sulphur atom to form the sulphonamide bond is increased by the presence of an animo group in the molecule. This is demonstrated by the synthesis of benzene sulphonyl amino methane sulphonic acid, from benzene sulphonyl chloride and amino methane sulphonic acid, as compared to the failure of *p*-acetamino benzene sulphonyl chloride to react with amino methane sulphonic acid under like conditions. There are reasons to believe that the amino group in the amino sulphonic acid molecule provides internal compensation for any possible electron deficiency on the central sulphur atom of the acidic group, suppressing any inclination on the part of the sulphur atom to play the role of electron-acceptor towards an external source of binding electrons. Furthermore, this postulated inactivating effect of the amino group may depend upon its proximity to the acidic function. Thus the α-amino alkyl sulphonic acids do not form sulphonamides. The β-amino alkyl sulphonic acids do form sulphonamides but only to a limited extent, demonstrated by the readiness with which tauryl chloride derivatives react with amino carboxylic acid esters as against their failure to couple with the less reactive free amino acids and with amino alkyl sulphonic acids. With still further removal of the amino group from the acidic function, the electrophilic character of the central sulphur atom continues to increase and the molecule becomes capable of undergoing "peptide" coupling even with a second amino alkyl sulphonic acid component. Thus Helfeirch and Otten[11] caused carbobenzoxy-δ-amino-butane sulphonyl chloride to react with 1,4-amino butane sulphonic acid to form the corresponding "dipeptide".

In contradistinction to the negative results obtained with the α-amino alkyl sulphonic acids, we did succeed in preparing some "peptides" containing a β-amino alkyl sulphonic acid component, viz. taurine. Thus we were able to prepare the ethyl esters of phthaloyl-tauryl-glycine, carbobenzoxy-tauryl-glycine and phthaloyl-tauryl-glycyl-glycine. In these "peptides" the esteric end group could not be split off by hydrolysis without decomposition of the compounds. In attempts at removal of the phthaloyl group by means of alcoholic hydrazine, reaction did occur, but the final products isolated could not be identified.

[6] J. R. Vaughan, Jr., *J. Amer. Chem. Soc.* **73**, 3547 (1951).
[7] J. C. Sheehan and C. P. Hess, *J. Amer. Chem. Soc.* **77**, 1067 (1955).
[8] Y. Liwschitz and A. Zilkha, *J. Amer. Chem. Soc.* **76**, 3698 (1954).
[9] E. Fischer, *Untersuchungen ueber Aminosaeuren, Polypeptide und Proteine* p. 326. Springer, Berlin (1906).
[10] W. Grossman and E. Wuensch, *Fortschritte der Chemie Organischer Naturstoffe* Vol. XIII, p. 452. Springer, Wien (1956); H. Gilman, *Organic Chemistry* Vol. I, p. 880. John Wiley, New York (1949).
[11] B. Helferich and G. Otten, *J. Prakt. Chem.* (NF), **1**, 2 (1954).

Hippuryl chloride reacts smoothly with amino methane sulphonic acid to give the appropriate "di-peptide", but the benzoyl group could not be split off by hydrolysis without rupturing the peptide bond. The desired free "di-peptide" was, however, obtained from the corresponding carbobenzoxy derivative by splitting off the protecting group with an anhydrous solution of hydrogen bromide in acetic acid.

α-N-(carbobenzoxy glycyl)-amino ethane sulphonic acid was obtained in small yield by the mixed anhydride method,[6] using isobutyl chloroformate as the coupling agent.

β-Alanyl amino methane sulphonic acid was synthesized by reacting phthaloyl-β-alanine with amino methane sulphonic acid in the presence of n-butyl chloroformate with subsequent removal of the phthaloyl group with alcoholic hydrazine, according to the method of Ing and Manske.[12]

Although *p*-acetamino benzene sulphonyl chloride did not couple with an amino alkyl sulphonic acid to give the "di-peptide", it did couple with β-alanine, to give *p*-acetamino benzene sulphonyl-β-alanine.

Most of the compounds prepared were tested for their inhibitory effect on the growth of micro-organisms. The results will be reported elsewhere.

## EXPERIMENTAL[13]

### *α-Amino-butane-sulphonic acid*

To 24 g sodium metabisulphite in 40 ml water, 23 ml (slight excess) butyraldehyde was added with stirring, cooled to 0° and 20 ml conc ammonia slowly added with continued stirring at room temp for 1 hr, cooled to 0°, and acidified with 1:1 HCl to pH 4. The crystals were filtered, washed with a little cold water, 50% ethanol and finally 96% ethanol. The air-dried product was recrystallized from 15 ml hot (60°) water, to give 2 g, m.p. 120–121°. (Found: C, 31·3; H, 7·1; N, 9·0; S, 20·4. $C_4H_{11}NO_3S$ requires: C, 31·3; H, 7·1; N, 9·1; S, 20·9%).

### *α-Amino-heptane-sulphonic acid*

The appropriate hydroxy sulphonate (19 g) was treated with 40 ml 1:1 ammonia, and the mixture warmed for ½ hr at 70°, filtered, cooled to 0° and acidified with conc HCl to pH 3. The pasty product was filtered, warmed with 50% ethanol and filtered. Yield 7·5 g (20%) m.p. 138–140°. (Found: C, 42·8; H, 8·9; N, 7·0; S, 16·3. $C_7H_{17}NO_3S$ requires: C, 43·1; H, 8·8; N, 7·2; S, 16·4%).

### *α-Amino-β-phenyl-ethane-sulphonic acid*

On attempting the preparation of this compound by treating the hydroxy sulphonate (obtained from redistilled phenyl acetaldehyde and potassium bisulphite) with conc ammonia, N,N-di-(benzyl methylene sulphonic acid)-amine, mono K salt was obtained. (Found: C, 43·4; H, 4·7; N, 3·4; S, 14·0; K, 8·7. $C_{16}H_{15}NO_6S_2K{\cdot}H_2O$ requires: C, 43·5; H, 4·5; N, 3·2; S, 14·5; K, 8·8%).

The required product was obtained by adding the hydroxy sulphonate portion-wise to a cold (0°) excess of ammonia with vigorous stirring. The mixture was stirred at room temp for 10 min. acidified with conc HCl to pH 3, filtered and washed with water, followed by ethanol. The product was purified by dissolving in the calculated amount of 8% bicarbonate solution, warming with addition of Norit, and acidifying the filtered solution with 1:10 HCl. After several hours in ice, a small quantity of white crystals was collected, m.p. 138–140°. (Found: C, 47·9; H, 5·6; N, 7·0; S, 15·9. $C_9H_{11}NO_3S$ requires: C, 47·8; H, 5·5; N, 7·0; S, 15·9%).

### *α-Benzoylamido-ethane-sulphonic acid, K salt*

To 5 g α-amino-ethane-sulphonic acid[3] in 40 ml 1:1 ethanol was added 6·9 g potassium carbonate and the mixture warmed to complete solution. Benzoyl chloride (8·4 g, 50% excess) was added to the cooled solution with stirring at 50° during 3 hr. The filtered solution was evaporated (water-bath) to

[12] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.* 2348 (1926).

[13] Melting points determined on Fischer–Jones Apparatus; microanalysis by Weiler and Strauss, Oxford, England.

first appearance of crystals, 20 ml ethanol was added and cooled. After 10 min, the crystals were collected. On recrystallization from hot water, the salt was obtained in 35% yield. (Found: C, 38·1; H, 3·9; N, 4·9; S, 11·4. $C_9H_{10}NO_4SK \cdot H_2O$ requires: C, 37·9; H, 4·2; N, 4·9; S, 11·2%).

*Benzoylamido-phenyl-methane-sulphonic acid, K salt*

This was obtained by benzoylation of phenyl-amino-methane-sulphonic acid[9] by the above method. (Found: C, 48·1; H, 3·7; N, 4·3; S, 9·6. $C_{14}H_{12}NO_4SK \cdot H_2O$ requires: C, 48·4; H, 4·0; N, 4·0; S, 9·2%).

*Carbobenzoxy-amino-methane-sulphonic acid, K salt*

To 111 g of amino-methane-sulphonic acid suspended in 250 ml water and cooled in ice, were added 69 g potassium carbonate. To the cold, stirred mixture was added simultaneously, during 40 min, 69 g potassium carbonate in 250 ml water and 150 ml of a solution of carbobenzoxychloride in toluene. (Bergmann and Zervas).[14] The mixture was stirred with cooling for 1 hr, followed by 4 hr at room temp. The product was collected, washed with water, ethanol and ether, yield 74 g (26%) m.p. 240–245°. (Found: N, 4·7; S, 10·8. $C_9H_{10}NO_5SK \cdot H_2O$ requires: N, 4·6; S, 10·6%).

*General preparation of α-benzylamino-alkyl-sulphonic acids*

To sodium bisulphite (0·25 moles) in 40 ml water was added at room temp one equivalent of the appropriate aldehyde, and after cooling (10–20°), a 10% excess of benzylamine in an equal volume of water. The mixture was stirred ½ hr at 50–70°, cooled, acidified with 10 N sulphuric acid to pH 4, placed in ice overnight and filtered. Where necessary, ethanol was added to the acidified solution to facilitate crystallization. After trituration with ethanol, the products were analytically pure without further recrystallization.

α-Benzylamino-β-phenyl-ethane-sulphonic acid was obtained by adding the appropriate hydroxy sulphonate to a 100% excess of 50% aqueous benzylamine. The product separated out initially as an oil.

The following compounds were prepared by the above method:

Benzylamino-methane-sulphonic acid; α-benzylamino-ethane-sulphonic acid; α-benzylamino-butane-sulphonic acid; α-benzylamino-iso-pentane-sulphonic acid; α-benzylamino-heptane-sulphonic acid; α-benzylamino-β-ethyl-hexane-sulphonic acid; benzylamino-phenyl-methane-sulphonic acid; benzylamino-*p*-anisyl-methane-sulphonic acid and α-benzylamino-β-phenyl-ethane-sulphonic acid.

The experimental data are summarized in Table 1.

TABLE 1. SYNTHESES OF α-BENZYLAMINO-ALKYL-SULPHONIC ACIDS

$$R{\cdot}CH(NH{\cdot}CH_2C_6H_5){\cdot}SO_3H$$

| R | M.p. | Yield (%) | Found (%) | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | C | H | N | S |
| H | 139 | 23 | 47·6 | 5·4 | 6·7 | 15·8 | 47·8 | 5·5 | 7·0 | 15·9 |
| $CH_3$ | 104–6 | 38 | 50·3 | 6·0 | 6·5 | 14·8 | 50·2 | 6·0 | 6·5 | 14·8 |
| $C_3H_7$ | 87–92 | 60 | 54·0 | 7·0 | 5·8 | 13·5 | 54·3 | 7·0 | 5·8 | 13·2 |
| $(CH_3)_2{\cdot}CH{\cdot}CH_2$ | 105–10 | 25 | 55·7 | 7·5 | 5·2 | 13·0 | 56·0 | 7·4 | 5·5 | 12·5 |
| $C_6H_{13}$ | 95–100 | 20 | 59·2 | 8·0 | 4·9 | 10·7 | 59·0 | 8·1 | 4·9 | 11·2 |
| $CH_3(CH_2)_3CH(H_5C_2)$ | 89–90 | 10 | 59·9 | 8·0 | | | 60·2 | 8·3 | | |
| $C_6H_5$ | 95–105 | 30 | 60·7 | 5·3 | 5·0 | 11·6 | 60·7 | 5·4 | 5·1 | 11·6 |
| $p$-$CH_3OC_6H_4$ | 100–104 | 30 | 58·3 | 5·3 | | 10·0 | 58·6 | 5·5 | | 10·4 |
| $C_6H_5CH_2$ | 84–85 | 20 | 61·6 | 6·0 | 4·8 | 11·3 | 61·9 | 5·9 | 4·8 | 11·0 |

[14] M. Bergmann and L. Zervas, *Ber. Dtsch. Chem. Ges.* **65**, 1192 (1932).

*β-Benzylamino-β-phenyl-ethane-sulphonic acid*

To 9·2 g 2-phenyl-ethene-1-sulphonic acid[15] in 40 ml water was added 15 ml benzylamine. After remaining at room temp for ten days and acidifying with 16 ml conc HCl, a heavy white precipitate separated, and on filtering, the desired product was obtained (40% yield), m.p. 184–186°. (Found: C, 61·6; H, 6·0; N, 4·7; S, 10·6. $C_{15}H_{17}NO_3S$ requires: C, 61·9; H, 5·8; N, 4·8; S, 11·0%).

N-*(benzoyl-glycyl)-amino-methane-sulphonic acid, K salt*

Amino-methane-sulphonic acid (5·6 g) was warmed with 25 ml 2 N potassium carbonate until evolution of $CO_2$ ceased. Hippuryl chloride[16] (9·9 g) and 25 ml 2 N potassium carbonate was added simultaneously during 1 hr to the cooled (0°) solution which was then stirred for 15 min, cooled, acidified with conc HCl and placed in ice overnight. Hippuric acid (1·7 g) was filtered and the filtrate concentrated in vacuo, yielding 9·7 g (63%) crude product, m.p. 235–250°. On recrystallization from water–ethanol, a pure product m.p. 258–260° was obtained. (Found: C, 36·9; H, 3·9; N, 8·4; S, 9·9. $C_{10}H_{11}N_2O_5SK \cdot H_2O$ requires: C, 36·6; H, 4·0; N, 8·5; S, 9·8%).

N-*(carbobenzoxy-glycyl)-amino-methane-sulphonic acid, K salt*

*Method* 1. Into a 250 ml flask fitted with a calcium-chloride tube, was introduced 10·5 g carbobenzoxy-glycine, 100 ml dry toluene and 5·1 g triethylamine. After cooling (−7°), 6·8 g isobutyl-chloroformate was added in one portion. The mixture kept at −10° for 20 min and then 5·6 g amino-methane sulphonic acid in 50 ml N potassium carbonate was added portionwise. After stirring vigorously at 0–10° for 1·5 hr, and for 2 hr at room temp, the aqueous layer was separated, washed with 3 portions of ether, acidified with 4·5 ml conc HCl and cooled in ice. After 4 hr, 7 g crude product, m.p. 150–170° was collected. The filtrate was concentrated and cooled, yielding 6·8 g (43%) of a pure product, m.p. 190–200°. Repeated recrystallization gave a product m.p. 208–210°. (Found: C, 38·5; H, 3·8; N, 8·1; S, 9·5. $C_{11}H_{13}N_2O_6SK$ requires: C, 38·8; H, 3·8; N, 8·2; S, 9·4%).

*Method* 2. To a mixture of 1·05 g carbobenzoxy-glycine and 1·03 g dicyclohexylcarbo-diimide[17] in 20 ml dry methylene chloride, was added 0·9 g (60% excess) amino-methane-sulphonic acid in 8 ml N potassium carbonate; 10 ml water was added and stirred at room temp for 7 hr. The dicyclohexyl-urea (1 g, m.p. 233–236°) was filtered, the aqueous layer separated, extracted with two portions of ether and acidified with 12 ml conc HCl to pH 1. After cooling, 500 mg of the desired compound, identified by mixed melting point, was collected.

*Glycyl-amino-methane-sulphonic acid*

Carbobenzoxy-glycyl-amino-methane-sulphonic acid (1·02 g) was treated with 5 ml HBr in glacial acetic acid (300 mg HBr/ml), and allowed to stand at room temp for 3 hr with frequent shaking. The small amount of undissolved material was filtered and the filtrate treated with ethanol to incipient cloudiness. The mixture was chilled, and the resulting flocculent precipitate coagulated. It was dissolved in 2–3 ml hot water and ethanol added until a gel separated, and on filtering and washing with ethanol, gave 100 mg of glycyl-amino-methane-sulphonic acid, which charred at 290° without melting. (Found: C, 21·3; H, 5·0; N, 16·4; S, 19·4. $C_3H_8N_2O_4S$ requires: C, 21·4; H, 4·7; N, 16·7; S, 19·0%).

N-*(carbobenzoxy-glycyl)-α-amino-ethane-sulphonic acid, K salt*

To a solution of 5·2 g carbobenzoxy-glycine in 50 ml dry toluene was added 4·6 g tributylamine, and, after cooling (−12°) 3·4 ml isobutyl chloroformate added in one portion. The solution was kept in a freezing mixture for 20 min, after which a solution of 3·1g α-amino-ethane-sulphonic acid[8] in 30 ml N potassium carbonate was added dropwise. The mixture was stirred (−5°) for ½ hr, 6 ml N potassium carbonate added, and stirring continued (1·5 hr). After filtering, the aqueous layer was separated extracted with 2 portions of ether and acidified with 5 ml conc HCl; 2 g carbobenzoxy-glycine was filtered and the filtrate concentrated in vacuo (40–50°) to first appearance of crystals. After cooling, filtering and washing with ethanol and ether, 800 mg of the potassium salt melting at

[15] F. C. Bordwell, C. M. Suter, J. M. Holbert and C. S. Rondestvedt, *J. Amer. Chem. Soc.* **68**, 139 (1946).
[16] E. Fischer, *Ber. Dtsch. Chem. Ges.* **38**, 612 (1905).
[17] G. Amiard and R. Heymes, *Bull. Soc. Chim. Fr.* 1360 (1956).

250–255° was obtained. (Found: C, 38·6; H, 4·5; N, 7·4; S, 9·0. $C_{12}H_{11}N_2O_6SK \cdot H_2O$ requires: C, 38·7; H, 4·6; N, 7·5; S, 8·6%).

*Phthaloyl-β-alanyl-amino-methane-sulphonic acid, K salt*

To a suspension of 22 g β-phthalimido-propionic acid[18] in 100 ml dry chloroform 14 ml triethylamine was added, and after cooling to −10°, 12·6 ml n-butyl-chloroformate was added. After standing (−5 to 0°) for 10 min, 11·1 g amino-methane-sulphonic acid in 50 ml 2 N potassium carbonate was added, stirred at room temp (2·5 hr) and filtered. After triturating with ethanol, 14·5 g (41%) of the salt, m.p. 266–268°, was obtained. After recrystallization (water–ethanol) the product melted at 268°. (Found: C, 40·9; H, 3·3; N, 8·0; S, 8·7; K, 11·0. $C_{12}H_{11}N_2O_6SK$ requires: C, 41·1; H, 3·1; N, 8·0; S, 9·1; K, 11·1%).

*β-Alanyl-amino-methane-sulphonic acid*

Phthaloyl-β-alanyl-amino-methane-sulphonic acid (7 g) in 30 ml water was refluxed with 20 ml N alcoholic hydrazine (1 hr), cooled, acidified with 2 ml conc HCl, and the phthalyl hydrazine filtered. After concentrating (vacuum) at 45–50° and diluting with ethanol, white crystals, giving a positive ninhydrin reaction, precipitated out, yield, 1·5 g, m.p. 283–285°. (Found: C, 26·2; H, 5·5; N, 15·2; S, 17·2. $C_4H_{10}N_2O_4S$ requires: C, 26·4; H, 5·5; N, 15·4; S, 17·6%).

*Carbobenzoxy-tauryl-glycine, ethyl ester*

Carbobenzoxy-tauryl-chloride[3] (2·8 g) was suspended in 1·4 g glycine ester HCl in 10 ml water; 1·7 g sodium bicarbonate was added, then 20 ml water and 10 ml ethanol. The mixture was stirred (room temp 6 hr), then left in ice (48 hr). Repeated recrystallization gave a small amount of white, tacky crystals. (Found: C, 48·5; H, 6·1; N, 7·8; EtO, 12·7. $C_{15}H_{20}N_2O_6S$ requires: C, 48·8; H, 5·8; N, 8·1; EtO, 13·1%).

*Phthaloyl-tauryl-glycine, ethyl ester*

Phthaloyl-tauryl chloride was prepared by refluxing potassium phthaloyl taurate[19] with 100% excess phosphorus pentachloride in benzene (water bath) for ½ hr. The phthaloyl tauryl chloride (84%) melted at 161–162°. (Found: N, 4·9; S, 11·9. Calc. for: $C_{10}H_6NO_4SCl$: N, 5·1; S, 11·7%).

Glycine ester HCl (14 g) in 50 ml 2 N potassium carbonate was added to 13·7 g phthaloyl-tauryl chloride in 100 ml benzene. After stirring (room temp 2 hr then 60° 3 hr), cooling and filtering, 8 g (57%) of white crystals, m.p. 126–127° were obtained. (Found: C, 49·2; H, 4·8; N, 8·1; S, 9·0; EtO, 13·2. $C_{14}H_{16}N_2O_6S$ requires: C, 49·4; H, 4·7; N, 8·2; S, 9·4; EtO, 13·2%).

*Phthaloyl-tauryl-glycyl-glycine, ethyl ester*

To 5·5 g phthaloyl-tauryl chloride in 35 ml benzene 4 g glycyl-glycine-ethyl ester HCl[20] was added followed by 1·1 g sodium carbonate in 5 ml water with stirring during 50 min. After stirring (4 hr) 2·8 g crude product was collected, dissolved in 60 ml ethyl acetate, filtered and precipitated with excess petrol ether. White crystals (1·2 g, 17%) m.p. 100–101° were obtained. (Found: C, 48·7; H, 4·6; N, 10·5; S, 7·7. $C_{16}H_{19}N_3O_7S$ requires: C, 48·4; H, 4·8; N, 10·6; S, 8·1%).

N-(p-*acetamido-benzene-sulphonyl*)-β-*alanine*

*p*-Acetamido-benzene-sulphonyl-chloride[21] (23·4 g) was added to a stirred solution of β-alanine (8·9 g) in 50 ml 2 N potassium carbonate, and then 2 N potassium carbonate (50 ml) added during 1 hr. After standing in ice (two weeks), 7 g (24%) crude product was filtered. After two recrystallizations (hot water), a pure product melting at 160° (slow heating) was obtained. (Found: C, 43·7; H, 5·3; N, 9·5; S, 10·1. $C_{11}H_{14}N_2O_5S \cdot H_2O$ requires: C, 43·4; H, 5·3; N, 9·2; S, 10·5%).

[18] S. Gabriel, *Ber. Dtsch. Chem. Ges.* **38**, 632 (1905).
[19] G. Pellizari and V. Matteucci, *Liebigs Ann.* **248**, 159 (1885).
[20] E. Fischer, *Untersuchungen ueber Aminosaeuren, Polypeptide und Proteine* p. 283. Springer, Berlin (1906).
[21] A. I. Vogel, *Practical Organic Chemistry* p. 871. Longmans, Green, London (1948).

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# SYNTHESIS OF ANALOGUES OF THE IRIDOLACTONES[1]

G. I. FRAY and Sir ROBERT ROBINSON
Research Laboratory, Shell Chemical Company, Egham

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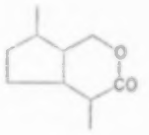
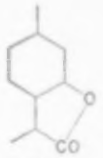
**Abstract**—Two stereoisomeric lactones of 2(2′-hydroxy-4′-methylcyclohex-1′-yl)propionic acid, analogues of the iridolactones, have been synthesized from D-citronellal.

FOLLOWING recent studies[2,3] on the synthesis of the iridolactones (I) from citronellal, the same starting material has been used to prepare two analogues, stereoisomers of structure (II).[4]

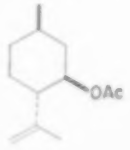



I

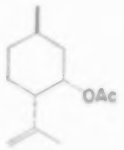



II

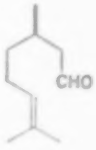
Isopulegyl acetate, obtained as a mixture of stereoisomers IIIa and IIIb[5] by the action[6] of acetic anhydride on D-citronellal (IV),[7] was oxidized with selenium dioxide in ethanol (cf. ref. 2), and the aldehydic product was treated with silver oxide in aqueous alkali to afford two stereoisomeric unsaturated hydroxy-acids, which were separated by crystallization.



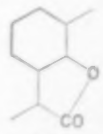

IIIa




IIIb



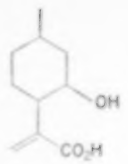

IV



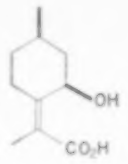

V

The infra-red spectra of these compounds clearly showed that they were $\alpha\beta$-unsaturated acids, but structure VI was ruled out by the absence of the band near 11·2 $\mu$ which is characteristic of the $CH_2$:CRR′ grouping.[8] The acids must therefore be represented by VIIa and VIIb.

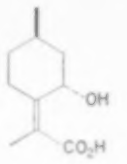
[1] The term iridolactones has been used[2] to cover both iridomyrmecin and isoiridomyrmecin.
[2] K. J. Clark, G. I. Fray, R. H. Jaeger, and Sir Robert Robinson, *Tetrahedron* **6**, 217 (1959).
[3] R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 15, 14 (1959).
[4] Since this work was completed, F. Korte, J. Falbe, and A. Zschocke, *Tetrahedron* **6**, 201 (1959), have published syntheses of a number of iridolactone analogues, including (V).
[5] *Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol. IIB, p. 521. Elsevier, Amsterdam (1953).
[6] F. Tiemann and R. Schmidt, *Ber. Dtsch. Chem. Ges.* **30**, 27 (1897).
[7] W. Klyne, *Progress in Stereochemistry* Vol. I, p. 189. Butterworths, London (1954).
[8] L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules* p. 58. Methuen, London (1958).




VI

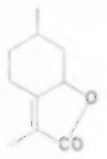



VII a

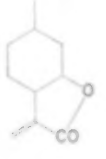



VII b

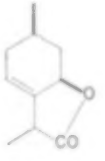
Treatment of the hydroxy-acids with hydrochloric acid yielded unsaturated lactones, of which the infra-red spectra each exhibited a carbonyl band (at 5·64 $\mu$) in the region characteristic of saturated $\gamma$-lactones,[9] indicating that the double bond was neither in the lactone ring as in VIII, nor in the exocyclic position as in IX. The structures of these stereoisomeric lactones were therefore considered to be Xa and Xb (the configurations of the $\alpha$-carbon atoms being uncertain).



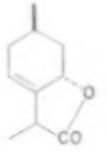

VIII




IX

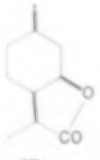



Xa

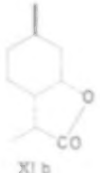



Xb

Hydrogenation of the unsaturated lactones finally afforded the corresponding saturated compounds, in which the lactone ring would be expected to be fused to the cyclohexane ring in the *cis* manner. The probable configurations of the saturated lactones were therefore XIa and XIb.




XI a




XI b

## EXPERIMENTAL

Unless otherwise stated, light petroleum refers to the fraction of b.p.40–60°. Infra-red spectra were determined for Nujol mulls.

*Stereoisomers of* 2(2′-*hydroxy*-4′-*methylcyclohexylidene*)*propionic acid* VIIa *and* VIIb

A solution of selenium dioxide (22 g) in ethanol (150 cc) was added during 1½ hr to a stirred mixture of isopulegyl acetate[8] $[\alpha]_D^{27}$ −1·30° (homog, 39 g) and ethanol (75 cc) at 50° (bath). The temperature was then raised to 95–100° for 24 hr, with continuous stirring. The reaction mixture was filtered, the filtrate evaporated, and the residue taken up in ether; the ethereal solution was washed with water and sodium hydrogen carbonate solution, and was dried and evaporated. Fractional distillation of the residue gave a pale yellow oil (8·9 g), b.p. 90–100°/0·2 mm. (Found: C, 68·2; H, 8·5. $C_{12}H_{18}O_3$ requires: C, 68·5; H, 8·6%). Gas chromatographic analysis showed that the fraction was a mixture. Attempts to isolate a pure aldehydic product by extraction with sodium hydrogen sulphite solution failed; the mixture was almost completely soluble, but could not be

[9] L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules* p. 186. Methuen, London (1958).

recovered by the addition of alkali or acid. The mixture was therefore used directly for the next stage.

A solution of sodium hydroxide (8 g) in water (250 cc) was added during 1 hr to a stirred mixture of the above aldehydic product (7·6 g), ethanol (100 cc), silver nitrate (14 g), and water (50 cc), and stirring was continued for 5 hr. The mixture was filtered, and the filtrate acidified with dil. sulphuric acid and extracted with ether. Extraction of the ethereal solution with sodium carbonate solution, followed by acidification, yielded a yellow viscous oil (4·2 g), which crystallized on trituration with light petroleum. Recrystallization from ether–light petroleum afforded an unsaturated *hydroxy-acid* as hard colourless prisms, m.p. 98·5–99°, $[\alpha]_D^{22}$ −37° (*c*, 1·17 in $CHCl_3$) (Found: C, 65·3; H, 9·1. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%). The infra-red spectrum showed bands at 2·92 (free O—H), 5·93 (conjugated C═O), and 6·13 $\mu$ (conjugated C═C).

The mother-liquors from the above crystallizations, on standing, deposited crystals (0·33 g) of m.p. 101–102° (depressed on admixture with the above hydroxy-acid of m.p. 98·5–99°). Recrystallization from benzene–light petroleum then yielded a second unsaturated *hydroxy-acid* as microscopic prisms, m.p. 102–103°, $[\alpha]_D^{26}$ −10° (*c*, 0·93 in $CHCl_3$) (Found: C, 65·2; H, 8·6%). The infra-red spectrum exhibited bands at 2·98, 5·89, and 6·15$\mu$.

*Stereoisomeric lactones of* 2(2′-*hydroxy*-4′-*methylcyclohex*-6′-*en*-1-*yl*)*propionic acid* Xa *and* Xb

(a) A solution of the hydroxy-acid of m.p. 98·5–99° (0·57 g) in hydrochloric acid (ca. 15%) was kept overnight, and then extracted with light petroleum. Evaporation of the solvent and recrystallization of the residue (0·23 g) from light petroleum (b.p. below 40°) at −10° gave the unsaturated *lactone* as flexible elongated prisms, m.p. 42–43°, $[\alpha]_D^{24}$ +63° (*c*, 0·99 in $CCl_4$) (Found: C, 71·9; H, 8·5. $C_{10}H_{14}O_2$ requires: C, 72·3; H, 8·5%). The carbonyl band in the infra-red spectrum appeared at 5·64 $\mu$.

On extraction of the remaining acidic solution with chloroform, hydroxy-acid (0·27 g) was recovered. Treatment as above then gave a further quantity (0·11 g) of the lactone.

Dissolution of the lactone (100 mg) in sodium hydroxide solution, followed by acidification with hydrochloric acid and extraction with chloroform, yielded the hydroxy-acid (105 mg), m.p. 98·5–99° (after crystallization), undepressed on admixture with a specimen of the original hydroxy-acid.

(b) Similar treatment of the hydroxy-acid of m.p. 102–103° (140 mg) afforded the unsaturated *lactone* (40 mg). Recrystallization from light petroleum (b.p. below 40°) at −10° gave elongated prisms, m.p. 31–31·5°, $[\alpha]_D^{24}$ +14° (*c*, 1·43 in $CCl_4$) (Found: C, 71·6; H, 8·5%).[10] The infra-red spectrum showed a carbonyl band at 5·64 $\mu$.

*Stereoisomeric lactones of* 2(2′-*hydroxy*-4′-*methylcyclohex*-1′-*yl*)*propionic acid* XIa *and* XIb

(a) The unsaturated lactone of m.p. 42–43° (105 mg) in ethanol was hydrogenated at atm press in the presence of 2% palladized strontium carbonate to afford the saturated *lactone* as colourless leaflets (100 mg), m.p. 49–49·5°, $[\alpha]_D^{27}$ +17° (*c*, 0·96 in $CCl_4$), after crystallization from light petroleum (b.p. below 40°) at −20° (Found: C, 71·2; H, 9·3. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9·6%). The infra-red spectrum showed a band at 5·64 $\mu$ corresponding to the carbonyl group.

(b) Similar hydrogenation of the unsaturated lactone of m.p. 31–31·5° (55 mg) yielded the saturated *lactone* (50 mg). Recrystallization from light petroleum (b.p. below 40°) at −20° gave microscopic prisms, m.p. 33·5–34·5°, $[\alpha]_D^{23}$ −5° (*c*, 0·98 in $CCl_4$) (Found: C, 71·1; H, 9·5%). The infra-red spectrum exhibited a carbonyl band at 5·64 $\mu$.

[10] Consistently low C values were obtained on repeated analyses.

Tetrahedron, 1960, Vol. 9, pp. 298 to 301. Pergamon Press Ltd. Printed in Northern Ireland

# BOOK REVIEWS

E. WALDSCHMIDT-LEITZ: **Chemie der Eiweisskörpper** (2nd Ed.). Ferdinand Enke, Verlag, Stuttgart 1955. 222 pp., 56s.

THE second edition of the book covers published work up to and including 1955. It follows the same general outline of the first edition whose main object was to introduce German readers to results published in other countries in a corresponding period. The emphasis throughout is again on the chemical rather than the physico-chemical or physiological properties of proteins. In this respect it is without doubt a worthy successor to the old edition and will be welcomed by the many chemists and biochemists who profited from the first edition. The vast amount of material—there are some 1650 references, many multiple—has been authoritatively and clearly reviewed. The numerous references to older work still important in modern development form an especially valuable contribution.

The five chapters in the first half of the book deal with amino acids as units of proteins, peptides, properties and reactions of proteins, hydrolysis of proteins and briefly with some points of protein structure. The rest of the book comprises only one additional chapter which is concerned with a more detailed discussion of the important members of the seven general groups of proteins, namely albumins, globulins, prolamines and glutelins, histones and protamines, sclero-, conjugated and physiologically active proteins. These discussions on individual proteins form valuable summaries not usually found in books of this type. The strict adherence to the chemistry of proteins produces certain anomalies. There is, for example, a detailed account of the chemistry of haemoglobins from different animals but no mention of the rather more interesting variants of human haemoglobin. Presumably this selection arose because at the time of writing differences in human haemoglobin were demonstrated largely by physical and not chemical techniques. However, this sort of thing must always arise where an author is concerned primarily with one particular aspect of a subject. In this case it in no way detracts from the success of the treatment of the main topic of the book.

E. M. SHOOTER

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A. M. LOVELACE, W. POSTELNEK and D. A. RAUSCH: **Aliphatic Fluorine Compounds.** American Chemical Monograph Series, Reinhold, New York, 1958. x + 370 pp., £5, $10.00.

ON the dust cover a very high claim is made, namely "complete coverage of all reported aliphatic fluorine compounds". This claim does not quite coincide with the statement of the authors themselves, who give a more accurate assessment of the book when they write in the Preface "The literature has been extensively reviewed from Moissan's time up to and including the year 1955. . . . However, every published paper on the subject is not included in the bibliographies, nor has every organic fluorine compound prepared been included in the tables. But quite a representative number of the contributions to the subject have been incorporated in the book". The work as a whole must indeed be considered as giving a most useful summary of the literature. The book is concerned with the treatment of the preparation and properties of different classes of aliphatic fluorine compounds. The first chapter describes various fluorination processes that may be employed for the introduction of fluorine into an organic compound. Each succeeding chapter is devoted to a specific class of aliphatic fluorine compounds namely fluoroalkanes, fluoroalkenes and fluoroalkynes, fluoroalcohols, fluoroethers, fluoroaldehydes and fluoroketones, fluorocarboxylic acids, acyl halides and fluoroanhydrides, fluoroesters, fluoronitrogen compounds, fluorometallic and organometalloidal compounds, fluorosulphur compounds.

Each chapter contains extremely useful tables (there are over 60 in all) describing the physical properties of fluorine compounds and giving an array of literature references.

The book is clearly printed and it is a simple matter to obtain quickly information about a

particular compound by reference to its empirical formula. The emphasis throughout is on synthetic methods and physical properties. This large compilation is not entirely free from misprints. In the statement, for example, on p. 37 "treated $CH_2FCH_2Cl$ with $PBr_3$ at 100° and obtained $CH_2FCH_2Br$," "$CH_2FCH_2Cl$" should read "$CH_2FCH_2OH$".

Although a large range of fluoronation methods is described, these are generally treated in a non-critical manner. This perhaps is not a drawback in a book which attempts to cover so much ground. The presentation is good and conforms to the usual high standards of American Chemical Society monographs.

It should be said that all workers in the fluorine field should possess this most valuable work of reference.

B. C. SAUNDERS

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MILOŠ HUDLICKÝ: **Chemie Organickych Sloučenin Fluoro**. Československe Akademie Ved., Prague 1958. 360 pp., Kcs 38,50.

THIS interesting book on organic fluorine compounds, written in the Czech language, is published by the Czechoslovakian Academy of Sciences. The reviewer would like to emphasis at the outset that a reader of no particular linguistic ability, but equipped with an inexpensive Czech dictionary will find no difficulty in translating this useful book even though it is written in one of the less known European languages. The author's style is simple and direct. Paragraphs are pleasantly short and the description of almost every chemical reaction is accompanied by an equation, which moreover indicates reagents, conditions and yields obtained. In addition, every equation is accompanied by a number giving reference to the original literature.

In an introduction, the author is at pains to point out that no single writer can cover the "full breadth and depth" of the subject and he therefore draws attention to a number of books on specialised aspects of fluorine chemistry. This list, though very useful, does not go beyond 1954. In general, literature references are complete up to 1956.

Ten chapters cover a wide range of topics in which both aliphatic and aromatic compounds are concerned. To begin with the author deals briefly with the history of fluorine chemistry and with safety measures required in laboratory work. The second chapter deals with the resistance of various materials towards fluorine and hydrogen fluoride. Then follows a chapter on fluorinating agents and one on methods of introducing fluorine into organic compounds. A chapter is devoted to details of the preparation of selected organic fluorine compounds.

A very useful chapter describes the more important reactions of organic fluorine compounds. Such processes as hydrogenation, reductions by sodium, zinc and lithium aluminium hydride, halogenation, nitration and hydrolysis are dealt with.

Physical properties are given in considerable detail, but only passing reference is made to the outstanding physiological properties of certain organic fluorine compounds.

Analytical methods are discussed and the final chapter deals with the practical applications of organic fluorine compounds.

It is usually the practice (quite correctly in the reviewer's opinion) of authors of original communications to place their names in alphabetical order at the head of a paper. Nevertheless this may often mean that the work of a senior author, whose name occurs late in the alphabet, may be difficult to trace in the general literature. To overcome this difficulty Dr. Hudlicky has given a subsidiary author index which enables the reader to trace the papers of a senior author when such papers are not immediately obvious in the main bibliography (which gives 806 references).

Every worker in the fluorine field should be in possession of this most useful book.

B. C. SAUNDERS

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JOHN C. SHEEHAN (Editor-in-chief): **Organic Syntheses.** Vol. 38. John Wiley, New York, 1958. vii + 120 pp., $4.00

OVER the course of the years few books have been of more importance to organic chemists throughout the world than the many volumes of *Organic Syntheses*. Not only have these books provided chemists with a large number of tested procedures for the synthesis of generally useful organic compounds,

but many of the methods serve as prototypes for related reactions. Also, the various volumes of the series have been richly furnished with examples of new techniques and descriptions of new apparatus of general utility. However, there has always been one serious deficiency, namely the lack of an explanation as to why some of the preparations have been selected for publication in *Organic Syntheses*.

It is obvious to all organic chemists why methods of preparation of such highly useful and interesting compounds as ketene (Collective Volume I), diazomethane (Collective Volumes II and III and Volume 36), ethyl ethoxymethylenemalonate (Collective Volume III) and ferrocene (Volume 36), among many others, were chosen for publication in the past. It is also clear why the preparations of compounds such as 1-methylisoquinoline, monovinylacetylene, and 2-vinylthiophene, and why the model procedures described in the preparations of 4-bromo-2-heptene, hendecanedioic acid, 1-nitrooctane and 1,4-pentadiene have been chosen for the present volume. However, it is something of a mystery, at least to this reviewer, why methods of preparation of compounds such as 2-amino-4 anilino-6-(chloromethyl)-*s*-triazine, 2-bromo-3-methylbenzoic acid, 5,5-dimethyl-2-*n*-pentyltetrahydrofuran, 5-formyl-4-phenanthroic acid, 3-hydroxytetrahydrofuran, 2-methyl-2,5-decanediol, *trans*-2-methyl-2-dodecenoic acid, 2-methylenedodecanoic acid, methyl hydrogen hendecanedioate, and α-phthalimido-*o*-toluic acid, all found in the present volume, have been chosen. This is not an argument that the choices are poor ones; rather it is an admission of ignorance on the part of the reviewer. The main point, however, is that henceforth there will be no mystery to anyone as to why the various preparations are selected. On p. vi of the present volume it is stated that "subsequent volumes of *Organic Syntheses* will have a fourth section in each preparation which will explain why the preparation is published in *Organic Syntheses*." This new feature will be a welcome addition, and, if the suggestion is not an impracticable one, the editors might also consider the possibility of devoting a few pages of the next volume to an explanation as to why many of the preparations in several of the more recent volumes were selected.

2-Benzylaminopyridine, 3-(*o*-chloroanilino)-propionitrile, benzyltrimethylammonium ethoxide, dibromoacetonitrile, dicyclopropyl ketone, diethyl methylenemalonate, diphenylacetaldehyde, N-ethyl-*p*-chloroaniline, 6-ketohendecanedioic acid, β-methylglutaric anhydride, methyl *p*-tolyl sulfone, monobenzalpentaerythritol, monobromopentaerythritol and *trans*-stilbene oxide are the other compounds for which reliable methods of synthesis are described in Volume 38 of *Organic Syntheses*.

WILLIAM E. MCEWEN

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**Absorption Spectra in the Ultra-violet and Visible Region** (Edited by L. LÁNG, in collaboration with J. SZÖKE, G. VARSÁNYI and M. VIZESY). Publishing House of the Hungarian Academy of Sciences, Budapest, 1959. VIII + 440 pp.

THE book consists of two volumes. The first volume (85 pp.) gives a theoretical and technical introduction (in German) while the second contains 170 absorption curves and tables, respectively, of 156 organic compounds, with English headings. (The English version of the introductory volume is in press.) The first volume deals with the following topics: The origin and formation of spectra; Application of the Franck–Condon principle to polyatomic molecules; Unharmonicity; Dissociation and predissociation; The form and shape of electron bond systems; Chromophoric groups (simple and conjugated chromophors); Complex compound; The role of the medium.

The following conversions and others are included:
I—Wavelengths and wave numbers; II—Wave numbers into wavelengths; III—Wavelengths into Fresnel units; IV—Wavelengths into kcal/mole; V—Transmission into extinction and absorption; VI—Summary of the abbreviations used throughout the book; VII—Tables for spectroscopic energy calculations.

The second volume as a loose-leaf file contains inter-changeable pages of absorption spectral data of 156 organic compounds in solution, and of 13 others in the gas phase. Numerous experiments have been carried out both in polar and unpolar solvents and at several pH values, respectively. The majority of spectra have been recorded with a Beckman DU spectrophotometer, while a minority—in particular the gas phase spectra—by a Zeiss QU 18 quartz spectrograph.

A collection of ultra-violet spectra is already available in the Landolt–Börnstein handbook but

there was a gap in recording spectral data independently until a manual of Robert A. Friedel and Milton Orchin appeared presenting 579 absorption curves in a separate volume. The disadvantage of this manual for European use arises from the fact that the wavelengths are given in inches and not in reciproque centimeters. On the other hand, only graphs are recorded without tables of wavelengths and maximum or minimum data. The Hungarian authors intend to fill this gap by recording curves as well as maximum–minimum tables.

American data of a great number of organic chemical spectra are being summarized in the edition of the National Bureau of Standards, Washington. The valuable comprehensive manual ought to be added to from time to time with further experimental material. The book reviewed here may serve this purpose by collecting spectral data gathered in the Eastern hemisphere. Unfortunately, the present volume is limited to spectra taken up in Hungary. Nevertheless, the intention of forthcoming volumes is to extend the realm of this monograph to include data from neighbouring countries. In this case, the collection will surely contribute in a considerable manner to mutual exchange of scientific information between different countries, for absorption spectra serve nowadays as practical physical constants in the everyday practice of the organic chemist.

The reviewer is convinced of the usefulness of this first series of spectral data publication, the more so since this fits very well into the frames of the intentions of the Pergamon Institute.

G. Fodor

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Tetrahedron, 1960, Vol. 9, p. 302. Pergamon Press Ltd. Printed in Northern Ireland

## A list of some of the papers to be published in future issues

R. FOSTER: The absorption spectra of molecular complexes.

HUANG YAO-TSENG: Experiments on the synthesis of substances related to tetracyclines.

A. T. BALABAN and C. D. NENITZESCU: Reactions catalysed by aluminium chloride—XXVIII. The reaction of cycloalkanes with carbon monoxide.

T. SKOWROŃSKA-SERAFIN and T. URBANSKI: Preparation of derivatives of amidineurea and their reactions.

E. CLAR, G. S. FELL, C. J. IRONSIDE and (in part) A. BALSILLIE: Benzologues and other derivatives of peropyrene.

TOKUO KUBOTA and KEN'ICHI TAKEDA: Studies on the steroidal components of domestic plants—XXI. The structure of rogagenin(3) onanhydrokogagenin.

G. WITTIG und E. BENZ: Triptycen aus Dehydrobenzol und Anthracen; zugleich ein Beitrag über Reaktivität von at-Komplexen.

G. E. LEWIS: Structures of the mono-acid cations of 4-aminoazobenzene and its derivatives.

E. CLAR and A. MCCALLUM: The significance of benzenoid rings for the stability of aromatic hydrocarbons.

R. HODGES and R. I. REED: The stereochemistry of manoyl oxide.

Y. SCHAAFSMA, A. F. BICKEL and E. C. KOOYMAN: Free-radical reactions involving sulphur compounds—III. Photolysis of aromatic disulphides.

M. ASGAR ALI and C. A. COULSON: On the stability of substituted diphenylenes.

P. SENGUPTA, S. N. CHOUDHURI and H. N. KHASTGIR: Terpenoids and related compounds—I Constituents of the trunk bark of *Melia azadiracta* Linn. and the structure of the ketophenol, nimbiol.

P. SENGUPTA, S. N. SENGUPTA and H. N. KHASTGIR: Terpenoids and related compounds—II. Investigations on the structure of nimbin.

P. BROCKLEHURST, the late A. BURAWOY and A. R. THOMPSON: The electronic spectra of *p*-terphenyl and its derivatives.

R. W. H. BERRY, P. BROCKLEHURST and the late A. BURAWOY: The effect of terminal nitro and amino groups on the electronic spectra of conjugated hydrocarbon system.

P. BROCKLEHURST and the late A. BURAWOY: The electronic spectra of thiobenzophenone and its derivatives.

S. OHSHIRO: Studies on the synthesis of hydrogenated quinolines and isoquinolines as analgesics—XVIII.

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